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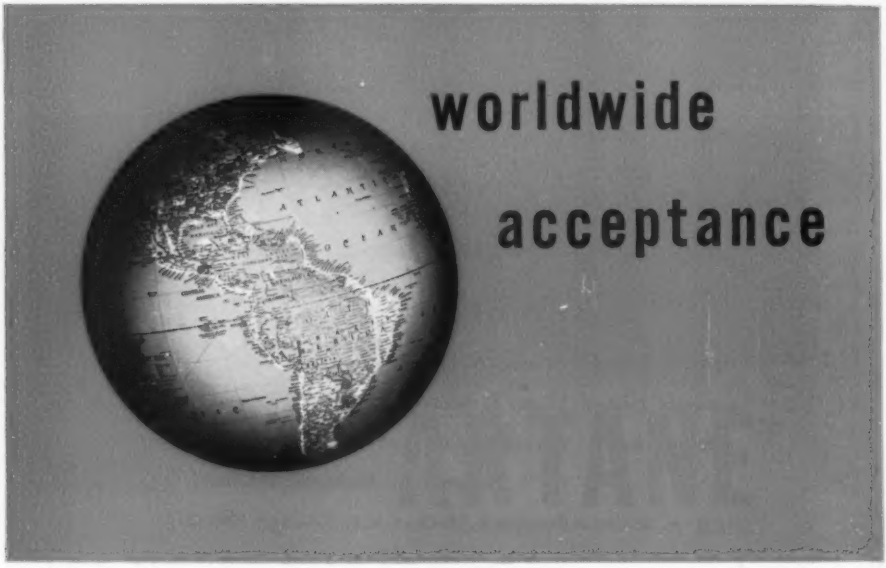

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INFORMATION FOR *Authors*

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WHAT ARE THE SIDE EFFECTS? Investigators have reported such symptoms as dizziness, nausea, weakness, drowsiness and epigastric distress in patients treated with Vesprin. Postural hypotension has been seen occasionally in normotensive patients. A hypotensive effect has been observed in patients with high blood pressure.
Anxiety and restlessness have been observed in some patients, and gain in weight in a few. These effects have usually been mild, and, as a rule have disappeared when the dosage was reduced or treatment stopped.
The most commonly encountered side effect has been the development of a Parkinson-like syndrome with motor disturbances and extrapyramidal symptoms. This syndrome is reversible and symptoms usually subside with a reduction of dosage or discontinuance of medication for 2 or 3 days.

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Caution: Although no deleterious effects on the hemopoietic system have occurred to date in the extensive clinical use of Vesprin, routine blood counts are suggested during the course of therapy.
Patients should be watched for indications of soreness of the mouth, gums or throat, or for symptoms of upper respiratory infection. If these complications occur, and a confirmatory leukocyte count indicates cellular depression, the agent should be stopped and appropriate treatment, including intensive antibiotic therapy, should be started immediately.

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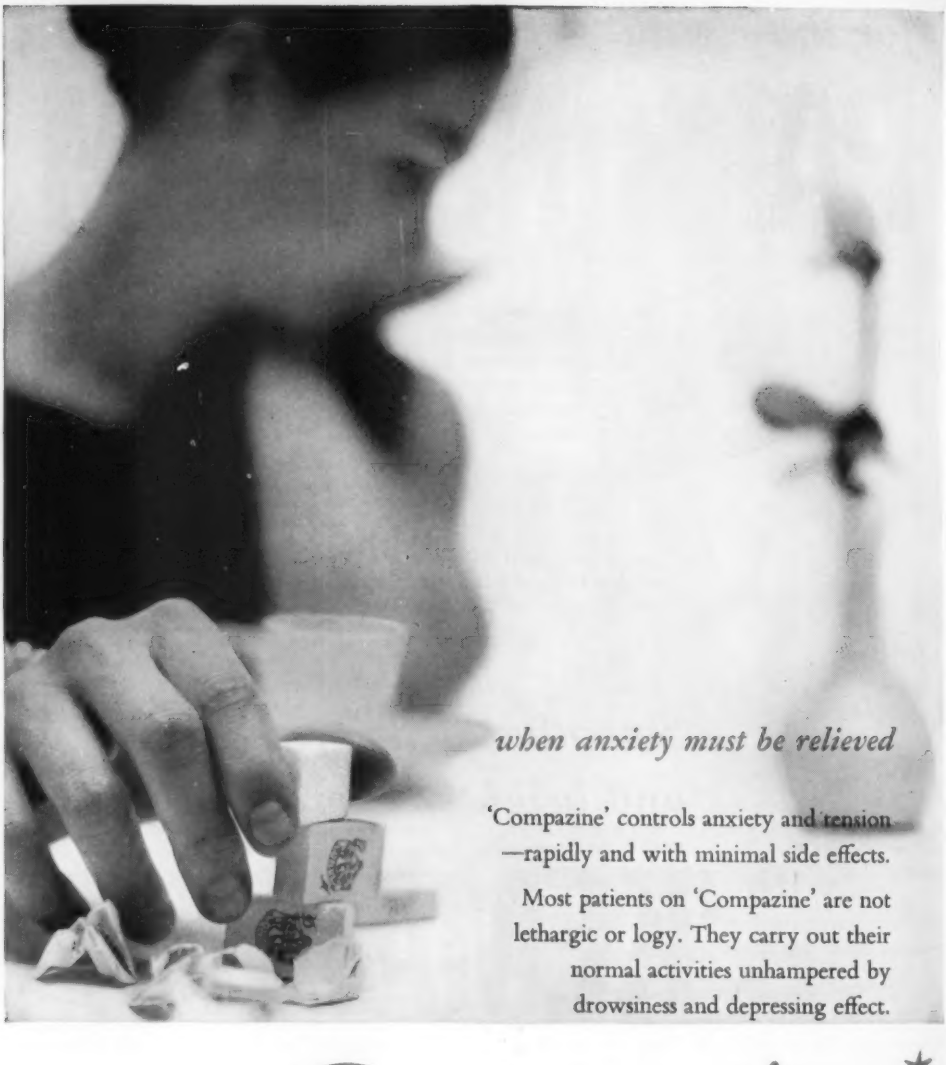

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Neurology Volume 7 • Number 12

Subdural Hematoma, Subdural Hygroma and Subarachnoid Hemorrhage Among Infants and Children

Robert W. Hollenhorst, M.D., Harold A. Stein, M.D., Haddow M. Keith, M.D. and Collin S. MacCarty, M.D.

DURING an 11 year interval at the Mayo Clinic, 47 cases of intracranial bleeding were encountered among infants and children.

The literature on this subject is extensive. One of the most interesting of the earlier reports was that of Rosenberg[1] in 1913. Sherwood[2] in 1930 published an excellent paper in which he summarized the older literature and presented nine cases of subdural hematoma among infants. His interest seems to have focused attention on this subject, since he stressed the importance of recognition and early therapy. Ingraham and associates[3–5] published reports on the largest series of cases and are largely responsible for our modern concepts of therapy of this condition.

Only a few reports on long-term studies of large numbers of infants and children afflicted with subdural or subarachnoid hemorrhage appear in the literature. The report of Ingraham and Matson[5] includes the largest number of cases (113) and is the most complete. Statten[6] reported on 28 cases and Elvidge and Jackson[7] reported on 55 cases. The paper written by Feferman and associates[8] contains an excellent summary of the literature, a discussion of pathologic factors, and the long-term results in 39 cases.

As we were principally interested in evaluating the ocular signs, symptoms, and visual prognosis when this paper was begun, more than the usual emphasis will be placed on such changes. These findings are being published elsewhere in more detail.

During the 11 year interval from 1945 through 1955, 54 patients five years of age or less were seen, in whom the diagnosis of subarachnoid hemorrhage, subdural hematoma, or subdural hygroma was made and proved by lumbar puncture, anterior fontanel puncture, or other neurosurgical procedures. Of the 54 patients, 47 were seen in consultation by a member of the section of ophthalmology, and only these 47 are included in this report. The eyes of these patients were examined under mydriasis with 2 per cent homatropine. Of the 47 patients, 31 had subdural hematoma, 10 had subarachnoid hemorrhage, and six had subdural hygromas.

GENERAL CONSIDERATIONS

Incidence. The incidence of intracranial bleeding is difficult to assess. The Mayo Clinic is the only neurosurgical center within a radius of some 90 miles, so that probably all patients in the immediate vicinity are seen in this institution. Eight of the patients seen in the 11 year period came from the city of Rochester itself. It is estimated that there are about 4,000 children five years of age or less in Rochester. This gives an incidence of slightly less than one case among 4,000 children in any one year.

Age and Sex. Thirty-nine of the 47 patients were less than one year of age. The mean age was six months, which is in agreement with the statistics given on all other large series of such

From the sections of ophthalmology, pediatrics, and neurologic surgery, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.
Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 27, 1957.

TABLE 1

INTRACRANIAL BLEEDING: SYMPTOMS AND SIGNS (47 CASES)

Manifestations	*Subdural hematoma*	*Subarachnoid hemorrhage*	*Subdural hygroma*	*Total number*	*Per cent*
Ocular abnormalities	20	7	1	28	59.6
Intraocular hemorrhage	16	7	1	24	51.1
Convulsions	12	4	3	19	40.4
Vomiting	9	4	2	15	31.9
Spasticity	5	1	1	7	14.9
Paralysis	4	2	1	7	14.9
Stupor	5	2	0	7	14.9
Enlarging head	5	0	1	6	12.7
Irritability	3	1	0	4	8.5

cases. Most authors who have written on this subject ascribe the bleeding to tears in the vessels of the midline structures, caused by a shifting of the brain in relation to the relative immobility of the bony covering. In many cases the tearing occurs during birth or possibly before the intracranial supporting structures are sufficiently well developed to withstand the stresses put upon them.

In this series, 31 patients were boys and 16 were girls, the ratio of boys to girls being 2:1. This ratio of males to females is slightly higher than the ratio of 1.7:1 reported by Ingraham and Matson.[5]

ETIOLOGIC ASPECTS

A positive or a probable history of trauma was noted in 23 of the 47 cases. Two patients had hemophilia and one had purpura. In the remaining 21 patients, no history relevant to a cause for intracranial bleeding could be elicited.

Symptoms and Signs. The presenting symptoms in order of frequency were as follows: convulsions, vomiting, spasticity, paralysis, stupor, enlarging head, and irritability (table 1). The presenting signs noted most frequently among the 31 patients with subdural hematoma were ocular abnormalities (64.5 per cent of cases) and convulsions (38.4 per cent). Of the ten patients who had subarachnoid hemorrhage, 70 per cent had signs pertaining to the eyes and 40 per cent had convulsions and vomiting. Of the six patients with hygromas, only 16.7 per cent had ocular manifestations, the most frequent signs being convulsions (50 per cent) and vomiting (33 per cent).

OCULAR FINDINGS

It is of interest and importance that the ocular manifestations were the most constant of the findings and occurred among 28 (59.6 per cent) of the 47 patients (table 1); 24 (51.1 per cent) of the 47 patients had intraocular hemorrhages. Sometimes merely a few hemorrhagic areas about the size of the optic disk or larger were seen in the retina. Usually, however, the retinal hemorrhages were so massive that they covered the entire posterior pole of the eye, obscuring most or all details of the ocular fundi. Among 24 patients who had intraocular hemorrhage, five had papilledema and five had palsy of the cranial nerves, two of both sixth nerves, one of the right sixth nerve, and two of the third cranial nerve. Two of the 28 patients who had ocular abnormalities had papilledema without retinal hemorrhage, and two had palsy of the sixth cranial nerve without retinal hemorrhage (table 2).

Of the 24 patients who exhibited intraocular hemorrhages, 17 had bilateral hemorrhages, four had bleeding into the right eye only, and three had bleeding into the left eye only. There was an equal sex distribution among those with and without intraocular hemorrhage. The presence or absence of intraocular hemorrhage statistically did not appear to be related to the severity of the presenting symptoms. Howev-

TABLE 2

OCULAR ABNORMALITIES IN INTRACRANIAL BLEEDING

Ocular abnormality	*Cases*	*Subdural hematoma*	*Subarachnoid hemorrhage*	*Subdural hygroma*
Retinal hemorrhage	24			
Alone		12	3	1
With papilledema		3	0	0
With extraocular muscle palsy		1	2	0
With papilledema and ocular muscle palsy		0	2	0
Extraocular muscle palsy	2	2	0	0
Papilledema	2	2	0	0
No ocular defects	19	11	3	5
Total	47	31	10	6

er, the preponderant ocular abnormalities were found among the patients who had either subdural hematoma (64.5 per cent) or subarachnoid hemorrhage (70 per cent), but such abnormalities were unusual among the patients who had subdural hygroma (16.7 per cent). Neither of the two patients who had infectious subdural hygromas had ocular signs.

Munro[9] stated that the division of subdural hematoma into acute and chronic forms was "unnecessary and artificial." We could not establish a correlation between the incidence of intraocular hemorrhage and the onset or duration of symptoms of the disease (table 3).

TABLE 3

RELATION OF ONSET OF SYMPTOMS TO RETINAL FINDINGS

Onset of symptoms	*Retinal findings*	
	Retinal hemorrhages	*Normal fundi*
Less than 24 hours	10	5
24 hours to 2 weeks	7	8
2 weeks to 2 months	5	8
Longer than 2 months	2	2

DIAGNOSIS AND TREATMENT

Diagnostic Procedures. The presence of subarachnoid hemorrhage was proved either by lumbar or fontanel puncture. All cases of subdural hematoma and hygroma were proved by subdural aspiration or craniotomy. Of the ten patients who had subarachnoid hemorrhage, one patient had hemophilia and one had purpura. Subdural hygromas, present in six patients, were bilateral in three, on the left side in two, and on the right side in one. Subdural hematomas in the 31 patients were bilateral in 22, on the right side in four, and on the left side in five.

Management. The ten patients who had subarachnoid hemorrhages were treated by rest in bed and repeated lumbar or fontanel puncture. The 37 patients who had subdural hematoma or hygroma were treated as follows: five by repeated subdural aspiration only, six by repeated aspiration followed by burr-hole evacuation of the hematoma, six by craniotomy and evacuation of the lesion, and 20 by repeated subdural aspiration followed by removal of the hematoma and membranes through craniotomy (table 4).

PROGNOSIS

Five patients died during the initial period of hospitalization, one died one year later, another two years later, and one about eight years later. Five of the eight patients who died had sustained severe trauma to the cerebral structures. Three of the five who died in the initial period of hospitalization were examined at necropsy. Among the seven who died within the first two years, one was a patient who had subarachnoid bleeding during the course of hemophilia, one had subarachnoid hemorrhage during the course of purpura, one died at the age of four days of a massive subarachnoid and intracerebral hemorrhage, one died after operation for removal of huge traumatic subdural hematomas, one died two weeks after craniotomy for removal of bilateral subdural hygromas, and one died of a skull fracture and severe cerebral contusions. One had a severe traumatic subdural hematoma on the right side; the membranes were removed and he died of unknown causes two years later.

Follow-up information was obtained on all but two of the 47 patients in this series. The

TABLE 4

TREATMENT AND PROGNOSIS

Condition and treatment	*No. of patients*	*Normal at time of follow-up*	*Residual defects*				*Deaths*	*Not followed*
			Severe	*Moderately severe*	*Moderate*	*Mild*		
Subdural hematoma or hygroma:								
Repeated subdural aspirations only	5	3*	0	0	0	1	1	0
Repeated subdural aspirations and burr-hole evacuation	6	4	0	1	1	0	0	0
Craniotomy and evacuation	6	2	0	1	0	0	3†	0
Craniotomy and removal of membranes	20	13*	3	0	0	1	1‡	2
Subarachnoid hemorrhage:								
Spinal and subdural aspirations	10	3	1	1	2	1	2§	0
Total	47	25	4	3	3	3	7	2

*One patient had infectious hygroma.
†Two patients had traumatic hygromas.
‡One patient had hygroma.
§One patient had purpura.

TABLE 5

DURATION OF FOLLOW-UP STUDY

Follow-up period	*Cases*
1 year	3
2 years	4
3 years	4
4 years	6
5 years	5
6 years	4
7 to 10 years	12

TABLE 6

FREQUENCY OF RESIDUAL DEFECTS

Defect	*Cases*
Ocular abnormalities	9
Mental retardation	8
Spastic paralysis	9
Speech difficulties	3
Convulsions	2
Required institutional care	3

survivors were followed from a year to ten years. Information recorded on repeated examinations at the clinic was supplemented by letters from the parents or attending physicians (table 5).

There were 38 patients who were traced and who had survived longer than two years (table 5). Of these, ten had permanent physical damage and three additional patients had isolated ocular defects. There were only three patients who were totally incapacitated and blind. One of the three died at the age of eight years. Nine children had various degrees of residual spastic hemiplegia; eight were mentally retarded and nine had ocular defects (table 6). Two had visual defects in one eye. Thus, of the original 45 patients in whom the outcome could be recorded, 25 (55.6 per cent) recovered completely and showed no signs of residual damage from the intracranial bleeding. If we exclude the seven patients who died during the first two years, the percentage of complete recoveries is 65.8 per cent.

Relationship of Ocular Signs to Prognosis. The grave prognostic implication of intraocular bleeding among adults who have spontaneous subarachnoid hemorrhage was pointed out by Manschot.[10–12] He found the mortality rate to be 50 per cent among those adults who had such intraocular complications, in contrast to a mortality rate of only 25 per cent among those whose eyes were normal.

Retinal and subhyaloid hemorrhages appearing during the course of intracranial bleeding among adult patients have been discussed in many published reports.[13–21] Among infants, their presence has been commented on particularly by Govan and Walsh,[15] Guthkelch,[22] Ingraham and Matson,[4,5] and Statten.[6] Smith[23] and Smith, Kearns, and Sayre[24] have discussed the pathologic and experimental aspects of these intraocular hemorrhages.

In addition to data on the mortality rate, we attempted to determine the relationship between intraocular hemorrhage and ultimate physical and mental outcome of the children.

As has been noted, 24 of the 47 children in our series had intraocular hemorrhages, and four others had either palsy of the sixth cranial nerve or papilledema without retinal hemorrhage. Follow-up information was not available on two of these 28 patients (table 7). Of the remaining 26 patients, three died, 11 were left with residual physical and mental damage, while 12 (46 per cent) were essentially normal. One of the severely incapacitated patients died about eight years later. Follow-up information was obtained on all 19 patients who did not have ocular abnormalities on initial examination. Of these, four died within the first two years, two had residual physical damage, while 13 (68.4 per cent) were completely normal.

Relationship of Initial Ocular Abnormality to Ultimate Binocular Vision. It is important to know that the prognosis for ultimate binocular vision is not uniformly good among those infants who have ocular abnormalities at the time of the initial examination. Our study showed permanent visual impairment among eight (34.8 per cent) of the 23 surviving patients who had initial ocular abnormalities and were followed, whereas permanent ocular defects were noted in only one (6.7 per cent) of the 15 survivors without initial ocular abnormalities. Seven of the eight patients had

TABLE 7

RELATIONSHIP OF OCULAR SIGNS TO PROGNOSIS

Condition of eyes on initial examination	*Traced cases*	*Follow-up information*		
		Died	*Permanent defects*	*Essentially normal*
Abnormalities present				
With retinal hemorrhages	22	3	9	10
Without retinal hemorrhages	4	0	2	2
Normal eyes	19	4	2	13
Total	45	7	13	25

TABLE 8
RELATIONSHIP OF DURATION OF SYMPTOMS TO PROGNOSIS

	Time since onset of symptoms			
	Less than 24 hours	*24 hours to 2 weeks*	*2 weeks to 2 months*	*Longer than 2 months*
Died or residual damage	7	6	4	3
Normal outcome	7	10	7	1

TABLE 9
PERMANENT PHYSICAL DEFECTS

Case	*Etiologic factor*	*Age at onset of symptoms*	*Condition*	*Treatment*	*Age (years) at last examination*	*Permanent defects*
			Severe defects			
1	Fractured skull (automobile accident)	11 mo.	Bilateral subdural hematomas; retinal hemorrhage, right eye	Craniotomy elsewhere and again at clinic 2 months later	8	Blind; paralyzed; incapacitated. Died, 8 years of age
2	Fractured skull (automobile accident)	2 mo.	Subarachnoid hemorrhage; retinal hemorrhage and palsy on right (third cranial nerve)	Repeated aspirations, subdural and spinal	3	Blind; bilateral optic atrophy; totally incapacitated; right hemiplegia; epileptic
3	Trauma at birth	2 mo.	Bilateral subdural hematomas	Trephines elsewhere, twice; craniotomy and removal of membranes at clinic	4½	Blind; spastic; cannot sit, walk, or talk
4	Unknown	9 mo.	Left subdural hematoma; choked disks; osteomyelitis of skull	Aspirations, trephine, removal of membranes	4½	Severe mental retardation (IQ 61) (moron); cannot walk or talk; right hemiplegia
			Moderately severe defects			
5	Trauma (fall)	17 mo.	Left subdural hematoma and subarachnoid hemorrhage; retinal hemorrhage and palsy (left third cranial nerve)	Spinal tap; trephines	9	Mental retardation (IQ 61) (moron); spastic (right) hemiplegia; severe amblyopia, left eye and left exotropia
6	Unknown	3 yr., but had had convulsions and left spastic hemiplegia since age 4½ mo.	Bilateral subdural hematomas; palsy (right sixth cranial nerve)	Trephines and craniotomy	5½	Mental retardation; spastic (right) hemiplegia; question of right homonymous hemianopsia; mild amblyopia and esotropia in right eye
7	Trauma at birth	4 days	Subarachnoid hemorrhage; retinal hemorrhages	8 spinal taps	7	Right spastic hemiplegia; speech difficulty
			Moderate defects			
8	Unknown	1 mo.	Left subdural hematoma; retinal hemorrhage	Repeated aspiration; then trephine	2½	Right spastic hemiparesis
9	Automobile accident	4 yr.	Subarachnoid hemorrhage; retinal hemorrhage; papilledema; palsy bilateral, sixth cranial nerve	Spinal taps	12	Mild mental retardation; defective vision
10	Unknown	1 wk.	Subarachnoid hemorrhage	Spinal and subdural aspirations	3	Mild spastic (right) hemiparesis; speech difficulty
			Mild defects			
11	Trauma at birth	2 days	Subarachnoid hemorrhage; retinal hemorrhage	Repeated aspiration, subdural and spinal	5	Esotropia; mild bilateral palsy (sixth nerve); mild mental retardation
12	Unknown	4 mo.	Right subdural hematoma; retinal hemorrhages	Repeated subdural aspiration	9	Esotropia; amblyopia, one eye
13	Fall	5 mo.	Bilateral subdural hematoma; retinal hemorrhages	Repeated subdural aspirations; later removal of membranes	9½	Severe amblyopia, one eye; very bright mentally

intraocular hemorrhage, two had palsy of the sixth cranial nerve, and two had palsy of the third cranial nerve.

Relationship of Age to Prognosis. Feferman and associates[8] conducted follow-up examinations on 28 of their 39 cases. They found that children who were less than six months of age when treated had a better outlook than did those who were older than six months when treated. We were unable to show such a relationship in our patients. An equal number died or had residual damage in each age group.

Relationship of Duration of Symptoms to Prognosis. As can be seen from table 8, there seemed to be little difference in the outlook of patients treated for periods varying up to two months after the onset of symptoms. However, three of the four patients whose symptoms were present longer than two months prior to institution of treatment had permanent damage to cerebral or visual structures.

Treatment. As noted in table 4, the majority of the patients who had subdural hematoma or hygroma were treated by craniotomy to evacuate the hematoma and remove the membranes to permit subsequent growth and development of the brain. Of the 20 so treated, one died, two could not be followed, three had severe residual defects probably due to associated severe cerebral damage, one had only an amblyopic eye, and 13 (72.2 per cent of those followed) were completely normal. Of the six treated by craniotomy and evacuation only, three died and one (case 6) had moderately severe residual defects, while only two (33.3 per cent) were normal (table 9). Of those who died, two had hygromas and one had subdural hematoma and intracerebral hematoma as a complication of hemophilia.

Six patients had burr-hole evacuation of hematoma. Two patients had residual defects (cases 5 and 8) (table 9). Four (66.7 per cent) had complete recovery.

Five patients were treated by subdural aspiration only. The patient who died had subarachnoid hemorrhage also. Three patients had residual defects (cases 2, 11, and 12) (table 9). Three (60 per cent) had complete recovery.

Of the ten patients who had subarachnoid hemorrhage, two died on the day of admission; one death resulted from purpura and the other from traumatic injury. Residual defects were noted in cases 2, 7, 9, 10, and 11 (table 9). Three patients (30 per cent) had complete recovery.

SUMMARY

A review of 47 cases of subdural hematoma, subdural hygroma, and subarachnoid hemorrhages encountered at the Mayo Clinic showed that the symptoms and signs consisted predominantly of retinal hemorrhage, palsy of the third (oculomotor) or sixth (abducens) cranial nerve, convulsions, vomiting, spasticity, paralysis, enlarging head, stupor, and irritability. Trauma seemed to be the chief cause, being recorded among 49 per cent of the cases.

Seven of the 47 patients died; 13 had residual physical defects ranging from severe to mild, and 25 (53.2 per cent) made complete recoveries.

The procedure of choice in treatment of subarachnoid hemorrhage appears to be repeated spinal taps, rest in bed, and observation. The recommended treatment of subdural hematoma and hygroma is initially repeated aspiration of the contents of the subdural space, followed by trephine evacuation of the hematoma or hygroma when the clinical condition warrants, and later by craniotomy and removal of the membranes.

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■ Every medical man has some system of pathology. But there are systems and systems. Besides scientific pathology there is a crude pathology, and there is, unfortunately, a metaphysical pathology. We have long heard that old maids' husbands are always well behaved, and on the same principle the pathology of those who do not make post-mortem examinations is often confident and definite. But the really important thing is to be accurate and precise, otherwise we confidently organize error in definite formulae. A man's pathology may be too definite in the wrong way, because he has not worked for himself at pathology. It may be only superficially and verbally definite and really crude. He who has made many post-mortem examinations is not so metaphysical in his explanations of the pathology of some of those cases of disease of which there is no known morbid anatomy. In looking carefully for himself into the coarsely concrete, a realistic habit of mind is produced in a person, and thus he avoids verbal explanations of those most difficult cases which are without known morbid anatomy — of those, for example, commonly called the Neuroses.

J. Hughlings Jackson in *Address on Pathology*, published in 1882.

Distribution of Carbon-14 Labeled Isoniazid in Brain

Charles F. Barlow, M.D., Joseph C. Schoolar, Ph.D. and Lloyd J. Roth, M.D., Ph.D.

PREVIOUS STUDIES have revealed that carbon-14 labeled isoniazid or its metabolites is distributed in the central nervous system according to a well defined pattern.[1] The distribution pattern was established by autoradiograms of brain slices and supported by radioassay of selected anatomic areas of brain. It was suggested that the demonstrated anatomic differences in concentration could well be related to quantitative differences in the capillary bed of the structures involved. The previous paper consisted of a brief account of the early phases of this work, while the present report is concerned with an expanded treatment of the isoniazid distribution data, including data at extended time intervals after injection, and a demonstration of the relationship of the carbon-14 isoniazid label to vascularity.

MATERIALS AND METHODS

Twelve adult cats were used in these experiments. Four were sacrificed one hour after intraperitoneal injection of radioactive isoniazid, two after four hours, two after six hours, two after 12 hours, and two after 24 hours. The carboxyl labeled isoniazid used in these studies was synthesized by the method of Murray and Langham[2] and had a specific activity of 0.031 mc./mg. The labeled drug was diluted with normal isoniazid in saline to a concentration of 2.5 mg./ml with a resultant activity of 34×10^6 d.p.m./ml. and 10 mg./kg. total drug was injected.

The animals were heparinized ten minutes before sacrifice. During anesthesia with Pentobarbital sodium, the chest was opened and perfusion with normal saline was begun in order to remove the vascular contents from the vascular bed of the brain. The aorta was cannulated and the descending aorta clamped. The right heart was opened to allow return of the perfusate. Fifteen hundred ml. of saline under pressure of 140 mm. Hg flowed through the system in approximately 15 minutes. In our hands this perfusion technic is about 99 per cent effective in removing blood from the brain.[3] Virtually complete removal of blood was considered essential to proper evaluation of parenchymal drug concentration, since the amount of radioactive substance is very high in blood in relation to brain.

The perfused brain was removed and placed in a deep freeze at minus 26° for one to two hours. Serial coronal sections of 2 to 3 mm. thickness were made freehand with a 10-inch razor blade, and selected slices of hemisphere and brainstem-cerebellum were chosen for autoradiography. The following grossly visible anatomic structures were dissected from the remaining brain tissue for carbon-14 assay: cerebral cortex (sensorimotor, primary optic and auditory, associational), cerebral white matter, thalamus, hypothalamus, lateral geniculate body, medial geniculate body, caudate nucleus, globus pallidus, hippocampus, cerebellar cortex, cerebellar white matter, inferior colliculi, central medulla, medullary pyramids, and spinal cord. Most of these areas can be dissected with considerable assurance, but dissection of the lateral geniculate body and globus pallidus was most difficult and uncertain at best.

Carbon-14 activity was measured in an open window gas flow Geiger counter using the direct plating technic following homogenization,[4] and calculated on a dpm./mg. of dry weight basis with appropriate correction for self-absorption. Because of the unavoidable variation in dosage from animal to animal, it was necessary to correct the results in terms of disintegrations per minute to a common factor. Consequently, in relating all the animals to one another for the time studies, we followed the suggestion of Brattgard and Lindquist[5] and expressed the activity as the ratio between the number of counts (corrected for self-absorption) measured in the specimen and the number of counts in the injected solution per kilogram of body weight. This resulted in an effective dose-weight correction. For the comparison of isoniazid concentration to vascularity data, it was necessary to relate the activity of all structures sampled to a sin-

From the division of neurology of the department of medicine and the department of pharmacology, University of Chicago, Chicago 37, Illinois.

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TABLE 1

DOSE-WEIGHT CORRECTED* COUNTS/MINUTE OF ISONIAZID CONCENTRATION AT SEVERAL TIME INTERVALS

Area	1 hour (average)	4 hour (average)	12 hour (average)	24 hour
Cerebral cortex	302.1	192.6	80.4	trace
Cerebellar cortex	292.1	183.0	91.9	"
Hippocampus	277.0	208.0	99.7	"
Hypothalamus	250.9	208.0	87.9	"
Caudate nucleus	240.9	147.1	74.8	"
Thalamus	240.2	180.1	89.8	"
Lateral geniculate	225.6	96.4	—	"
Inferior colliculus	187.6	136.6	66.3	"
Medulla (central)	155.5	117.0	69.2	"
Globus pallidus	156.0	118.4	64.5	"
Cerebral white	152.8	128.2	58.5	"
Cerebellar white	143.9	126.0	56.2	"
Pyramids	122.7	89.7	51.7	"
Spinal cord	119.7	109.5	50.1	"

*$\frac{\text{counts/minute/mg. tissue}}{\text{counts/minute/Kg.}} \times 10^{-8}$

gle area of brain. The medullary pyramid was chosen for this purpose because it could be dissected with considerable assurance and regularly contained low activity. This relationship was established by means of the ratio

$$\frac{\text{"x" area activity}}{\text{pyramids activity.}}$$

Autoradiograms were made by a method previously described,[1,3] with an exposure time in the deep freeze at 26° C. for three months. It has been found that an important increase in the number of satisfactory autoradiograms can be obtained by a modification of the technic as it has been described in other communications. The smooth cut surface of the brain slice should be kept in the deep freeze in a box containing Drierite ($CaSO_4$) for ten or more days. This desiccates the surface to a slight degree and apparently eliminates the self-absorption of radioactivity due to ice formation on the surface of the block.

After development of the autoradiogram, photographs were made of all tissue slices in order to have a permanent record of the surface marking for easy anatomic comparison. Finally, histologic sections were made from the tissue blocks for further anatomic control.

The data on relative vascularity in the various structures of the cat brain were obtained by densitometric measurement of autoradiograms of animals injected with iodine-131 labeled serum albumin which remains within blood vessels and does not penetrate into the central nervous system. Details of this technic are reported elsewhere.[3] It will be noted that vascularity information is also reported in relative terms and all anatomic structures again are related to the white matter.

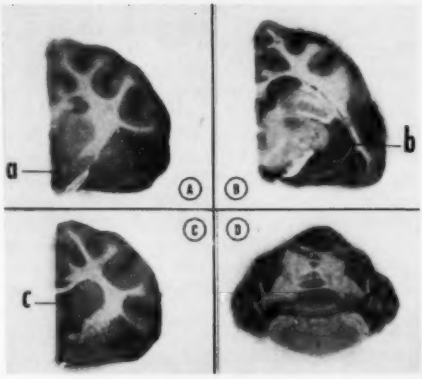

FIG. 1. A series of autoradiograms at four different levels of brain one hour after injection of carbon-14 labeled isoniazid with exposure time of 90 days. It will be noted that there is an easily visible pattern of differential density. Attention is directed to the high concentration of radioactivity in hypothalamus (a), hippocampus (b), and caudate nucleus (c), as well as in cerebral and cerebellar cortex.

OBSERVATIONS

Table 1 shows the average values from different structures of brain at different time periods following the injection. Autoradiograms illustrate and support the counting data (figure 1). It will be noted that the radioactivity gradually falls off and only a trace remains at 24 hours. The data from cats sacrificed after six hours did not contribute useful additional information and are not included in the table. The data from the four areas of cortex did not vary significantly from one another and were, therefore, averaged and handled as one structure. Table 2 illustrates the ratio of each area to the medullary pyramid. In figure 2 the ratios from certain illustrative areas are plotted against time. This illustrates that the various anatomic structures of brain tend to fall into three groups. The medulla and other regions of low activity, such as cerebral white matter, cerebellar white matter, globus pallidus, and spinal cord, tend to maintain a ratio near unity throughout the entire 12 hours postinjection. Most other areas of brain, as exemplified by cerebral and cerebellar cortex in figure 2, begin with a highest level at one hour and gradually decline. On the other hand, in hippocampus, showing a considerable concentration of activity at one hour, the ratio actually increases and is well maintained to 12 hours

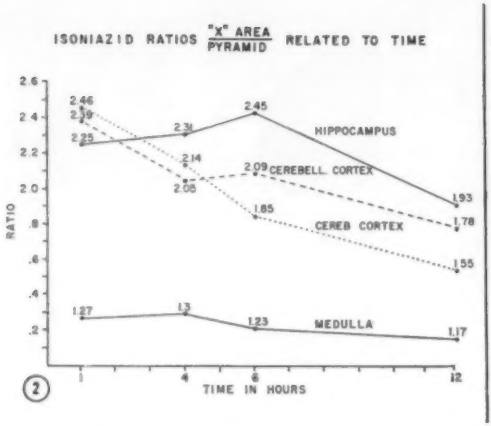

FIG. 2. Isoniazid ratios $\frac{\text{"x" area}}{\text{pyramid}}$ related to time showing the relative increase of carbon-14 label in hippocampus, while the ratios of such structures as cerebral and cerebellar cortex are decreasing.

FIG. 3. The ratio of INH (isoniazid) in a number of brain structures is compared with the ratios of vascularity. The greatest differences are seen in hippocampus where isoniazid is found in high concentration relative to vascularity and in lateral geniculate and inferior colliculus where the reverse is true.

although at this point it has begun relatively to decline.

Figure 3 shows the relationship of illustrative areas to vascularity ratios. There is a rough general relationship between carbon-14 concentration and the vascularity in many areas, such as cerebral and cerebellar cortex and medulla. However, the lateral geniculate body and inferior colliculus, which have the greatest vascularity as measured by the iodine-131 technic, have distinctly lower isoniazid concentrations. The hippocampus and, to a lesser extent, the hypothalamus, caudate nucleus, and thalamus contain the carbon-14 label in considerable concentration relative to their vascularity. This point is further illustrated by reference to the autoradiograms (figure 4).

DISCUSSION

A number of distribution studies of drugs in brain have been done in the past. It would not be appropriate to review this literature in detail, but reference to some of the work is pertinent. In an early study of a number of preparations by Veit and Vogt[6] with determinations in a number of areas of brain of dogs and cats by chemical and biological methods, the general conclusion was reached that the differences in distribution were largely conditioned by blood supply. The hippocampus and hypothalamus were not included in the determinations. Mayer and Bain,[7] in a study of the convulsant drug 10-(2-dimethylaminopropyl)-9-acridone in rats and cats, tended to attribute the differential distribution to the number of nerve cells, but of special interest to this study is the contrasting observation that hippocampus contained acridone in about half the concentration of cerebral cortical areas. In studying the distribution of isotopic bromine-82, Brattgard and Lindquist[5] demonstrated a greater relative concentration of this substance in cerebellar cortex of cats than can be accounted for on the basis of difference in vascular supply and were inclined to attribute the local concentration in cerebellum to a difference in blood-brain permeability in that region. Hippocampus was not included in the study. Miller and Elliot[8] examined the distribution of carbon-14 labeled morphine, codeine, and methadon in rats by counting and autoradiographic technics. Autoradiograms showed high activity only in the choroid plexus, but counts showed some interesting differences in areas with morphine, which apparently tended to concentrate early in spinal cord and hypothalamus. Specific study of hippocampus was not done. Maynert and Van Dyke,[8] working with nitrogen-15 labeled barbital in dogs, found no concentration difference in the various structures selected, which in itself is surprising in view of the differences usually found between gray and white matter.

TABLE 2

ISONIAZID RATIOS, $\frac{\text{"X" AREA}}{\text{PYRAMID}}$, AT THREE TIME INTERVALS

Area	*1 hour*	*4 hour*	*12 hour*
Cerebral cortex	2.46	2.14	1.55
Cerebellar cortex	2.39	2.05	1.78
Hippocampus	2.25	2.31	1.93
Hypothalamus	2.04	1.99	1.70
Caudate nucleus	1.96	1.64	1.45
Thalamus	1.96	2.00	1.73
Lateral geniculate	1.84	1.61	—
Inferior colliculus	1.53	1.52	1.28
Medulla (central)	1.27	1.30	1.17
Globus pallidus	1.27	1.32	1.23
Cerebral white	1.29	1.42	1.13
Pyramids	1.00	1.00	1.00
Spinal cord	0.98	1.22	0.97

Wase and co-workers[9] studied sulphur-35 chlorpromazine which was found to accumulate in the hypothalamus of rats. The last two studies did not include hippocampus. Finally, Benson, in association with the authors and utilizing similar autoradiographic technics, has shown that sulphur-35 labeled carbon disulfide localizes predominantly in the white matter, a fact that has been interpreted as a manifestation of the lipid solubility of this substance.[11] This fairly complete sampling of the literature in this field reveals some intriguing findings. Although there are many similarities in the distribution of drugs, probably accountable on the basis of general differences of vacular supply and metabolic activity in the various areas of brain, many of them also reveal distinct individual peculiarities in distribution.

The data presented here would suggest that factors other than vascularity of the various anatomic areas of brain are of importance in conditioning the distribution of isoniazid or its metabolic break-down products in this organ. The most vascular areas of cat brain such as inferior colliculus and lateral geniculate body contain relatively less carbon-14, while the hippocampus with generally relatively low vascularity has a high concentration of labeled drug. The situation relative to hypothalamus, caudate nucleus, and thalamus is less definite, but suggestive. There is a complicating factor relative to the vascularity of the hypothalamus. It is well known that the supraoptic and paraventricular nuclei of this structure are easily the most vascular areas of brain by a considerable margin.[12] However, these nuclei are so small in the cat that their presence is not revealed in our iodine-131 autoradiograms. It would seem that our figure for vascularity of hypothalamus of cat relates to the major portion of this structure, however, and probably is generally meaningful. It is also important to point out that, although the absolute values of the ratio of isoniazid concentration and vascularity are in the same range, the two sets of figures are out of step. It is this fact that is most significant. In comparing our vascularity figures with the regional blood flow data of Landau and associates,[13] it is immediately apparent that the magnitude of the ratio difference between cortex and white matter, for example, is much greater in the blood flow figures, but the essential similarity is that the anatomic areas stand in similar relationship to one another.

A limitation which should not be neglected in a study of this kind with isotope labeled drugs is the fact that we detect only the carbon-14 by our methods and cannot accurately equate this with assurance to the presence of the isoniazid that was administered. To be precise, it is more appropriate to refer to the carbon-14 in tissue as representative of isoniazid and/or its metabolites. These data seem to show that there is something physiologically different about the relationship of hippocampus to this drug or its metabolites.

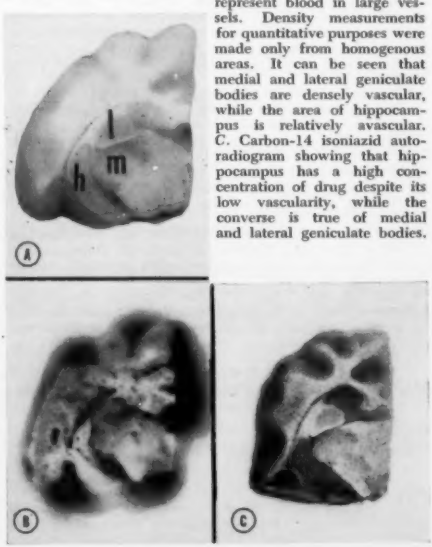

FIG. 4. Series of three photographs of comparable brain levels chosen to illustrate the relationship of isoniazid concentration to vascularity. *A.* Formalin-fixed coronal slice at level of medial (m) and lateral (l) geniculate bodies, and hippocampus (h). *B.* Iodine-131 autoradiogram illustrating vascular density. The very dark areas and spots represent blood in large vessels. Density measurements for quantitative purposes were made only from homogenous areas. It can be seen that medial and lateral geniculate bodies are densely vascular, while the area of hippocampus is relatively avascular. *C.* Carbon-14 isoniazid autoradiogram showing that hippocampus has a high concentration of drug despite its low vascularity, while the converse is true of medial and lateral geniculate bodies.

The factors that make for this difference are unknown. Relative to this point, an interesting chemical peculiarity of hippocampus is the unexpectedly high concentration of ascorbic acid in this area with respect to other areas of cerebral cortex in adult man and other animals, but no analysis was made of cat brain.[14] It has also been suggested by Manthei[15] that administration of ascorbic acid can be influential in the metabolism of isoniazid, altering its excretion and increasing its concentration in tissues generally.

We do not mean to imply that the site of greatest drug concentration is necessarily its site of major action. We view this investigation largely as a study of the dynamics of drug distribution in brain. It would seem, however, that these findings and the suggestions from studies cited in the literature contribute to the concept of a chemical and metabolic topography in the central nervous system, in addition to its well known physiologic and anatomic topography. It is also quite possible that this distribution pattern is by no means unique for isoniazid and that hippocampus behaves in this manner with a number of other substances. Further studies with other radioactive substances now in progress should resolve this question.

SUMMARY

1. The distribution pattern of carbon-14 labeled isoniazid in the central nervous system of cats was determined by radioassay of dissected tissue samples and autoradiography at several time points following injection of the drug. A well defined and consistent pattern of distribution from animal to animal was revealed.

2. Attempts to relate the local concentration of carbon-14 label to local vascularity in the central nervous system disclosed general agreement for some areas, but gross inconsistencies in others. The labeled drug was present in high concentration in hippocampus despite relatively lower vascularity, while the opposite was true in the geniculate bodies and inferior colliculi which are regions of high vascularity in the cat.

3. Hippocampus was unusual in another respect in that the relative concentration remained high throughout 12 hours, while the relative concentration in other areas of brain was falling.

4. It is concluded that factors other than local vascularity condition the distribution of this drug in the central nervous system of cats. These factors are not understood at present.

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Spinal Epidural in Hemangioma in Pregnancy

William S. Fields, M.D. and J. Randolph Jones, M.D.

HEMANGIOMA of the vertebrae is a fairly common lesion, but seldom produces clinical symptoms. Hammes reported that in a series of 10,000 consecutive necropsies at the Schmorl Institute, routine section of the vertebrae revealed an incidence of 10 per cent. However, since the first case with cord compression was described by Gerhardt[2] in 1895, less than 100 cases with neurologic involvement have been reported in the world literature.

Why the symptomatology varies so much from the anatomic involvement is still not clear. For instance, Junghanns[3] indicated that, although the entire vertebral body, and in some cases the neural arch as well, might be involved by the lesion, only a small number of his cases presented clinical evidence of spinal cord compression. Furthermore, an epidural lesion involving one or more spinal segments may be present without any roentgenographic abnormality.

It is noteworthy that, although only three-fifths of the vertebral hemangiomata encountered in Schmorl's laboratory were in the thoracic spine, proved epidural extensions of such lesions have been found only in the thoracic region.

Epidural hemangiomata are seldom encountered by neurosurgeons. Rasmussen and others[4] reported only 28 among 557 intraspinal neoplasms in the records of the Mayo Clinic, and Elsberg[5] noted four in his personal series of 85 epidural spinal tumors.

Vertebral lesions of vascular origin are almost always of the well-differentiated type and epidural extension of such lesions are similarly mature. On the other hand, epidural vascular neoplasms are usually of the mature type as well, but may on occasion be less differentiated tumors, such as hemangio-endothelioma or hemangioblastoma.

The case reported here is of particular interest in the respect that clinical manifestations did not occur until the third trimester of the patient's first pregnancy. Such a relationship as this, in which a vascular tumor of the spine and/or spinal cord has been noted as a complication of pregnancy, is extremely rare. This case will be reported in detail and four other cases from the literature cited briefly.

CASE REPORT

A 30 year old white female, primigravida, was admitted to Hermann Hospital for the first time on October 26, 1953. She was already three weeks past her expected date of confinement. She stated that in the early part of August, during the sixth month of her pregnancy, while swinging a tennis racquet, she suddenly experienced a pain between her shoulder blades which radiated anteriorly around her chest. This pain persisted for about 48 hours and then subsided completely. About six weeks later, she began to notice weakness in her knees and on two occasions she collapsed to the floor. This weakness gradually increased, and after about seven to ten days she noted numbness up to her waist. There was also some difficulty in walking at night without stumbling. The last week prior to hospital admission was spent in bed. For about two weeks she had been extremely constipated and had also had difficulty in starting her urinary stream.

Neurologic examination revealed increased muscular tone in both lower extremities with hyperactive tendon reflexes. There were bilateral patellar and ankle clonus and bilateral Babinski signs. Superficial abdominal reflexes were absent bilaterally. Pain and temperature sensation were absent over the lower extremities and trunk up to the D-8 level, bilaterally. Light touch was intact, but position and vibratory sensation were diminshed in both lower extremities below the knees.

Because of cephalopelvic disproportion, as well as the neurologic difficulty, the patient was delivered by cesarean section of a normal, healthy 9 lb. 7½ oz. male infant on October 27 under general anesthesia.

Following delivery, the bowel and bladder disturbance subsided. She began to gain some return of strength in her left lower extremity and experienced a burning sensation in her feet. Ten days following surgery, she began to appreciate some itching around the abdominal incision.

Lumbar puncture performed on November 1 showed a complete manometric block and a protein of 392 mg. per cent, negative Wassermann, and colloidal gold curve 0000011110. X-rays of the thoracic spine on November 3 showed a hemangioma of D-6 involving the body, pedicles, and the neural arch as well, on both sides. The adjacent vertebrae appeared to be normal.

The patient was discharged from the hospital on November 7 to continue convalescence at home.

From the divisions of neurology and neurological surgery, Baylor University College of Medicine, Houston, Texas.
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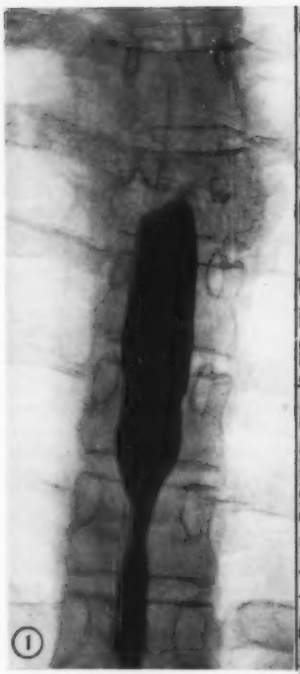

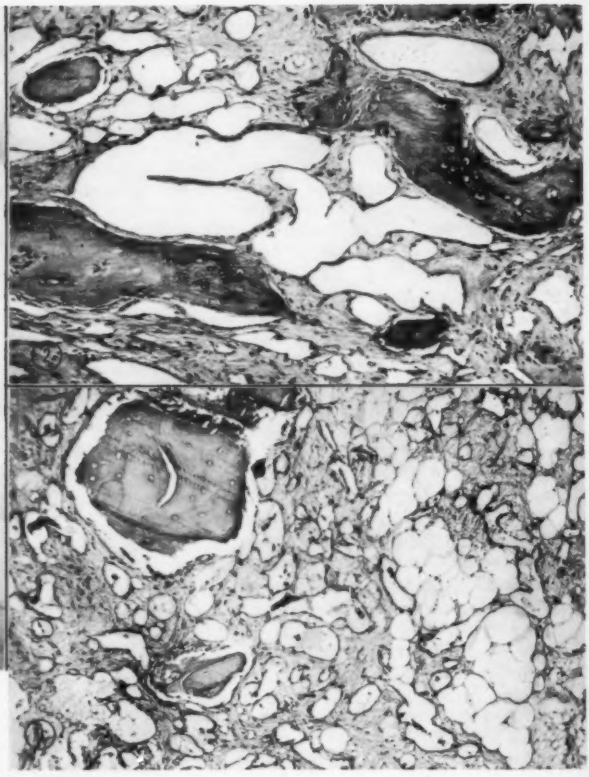

FIG. 1. Myelogram showing block compatible with an epidural lesion opposite body of D-6. Hemangioma of D-6 involving body, pedicles, and neural arch.

FIG. 2. Cavernous hemangioma of lamina of D-6.

FIG. 3. Hemangiolipoma, epidural, consisting of numerous endothelial-lined channels, adipose tissue, and ectopic bone formation.

Second admission. Because the patient's improvement seemed to reach a plateau after she had gone home, she was readmitted on November 22, 1953. On the day of admission a myelogram was performed which showed a complete block at the level of the body of D-6.

Operation (November 25). A midline incision extending from approximately D-3 to D-8 spinous processes was made and the erector spinae muscles dissected from the spinous processes and laminal arches over D-6 and approximately one laminal arch above and below. After dissecting the muscles from the spinous processes and the laminal arch, the arch of D-6 was noted to have a bluish discoloration due to markedly increased vascularity. This spinous process and laminal arch were carefully removed. After removal, a firm, partly calcified epidural mass of fatty tissue was found completely filling the epidural space and compressing the cord below the hypertrophied D-6 arch. This mass was dissected from the canal, necessitating partial removal of the lamina of D-5 in order to expose all of the indurated epidural fatty tissue. After this was removed, the dura was found to appear normal with no evidence of infiltration from the tumor and was pulsating freely. Hemorrhage was controlled with electrocoagulation and bone wax. The patient withstood the procedure well, with essentially no loss of blood.

Pathologic diagnosis. 1. Hemangioma, predominately cavernous, lamina, D-6. 2. Hemangiolipoma, epidural, with ectopic bone formation.

By December 1, 1953 the patient was much improved, was ambulatory, and showed only moderate weakness of both lower extremities with slight spasticity. The Babinski signs had disappeared, but there was still transient left ankle clonus. Hypalgesia to about D-8 remained bilaterally. She was discharged on this date.

Third admission. On October 8, 1955 the patient was admitted because of a spontaneous miscarriage of a three to four month old macerated fetus. She was discharged to her home two days later and made an uneventful convalescence.

Fourth admission. November 15, 1956. The patient entered the hospital for cesarean section two weeks prior to the expected date of confinement. This was carried out under general anesthesia and the patient delivered a normal female infant weighing 7 lb. 5 oz. At no time during the second pregnancy or puerperium did she have any neurologic difficulty. No residua of the neurologic deficit encountered during the first admission were apparent at the time of her last admission. She was discharged on November 25, 1956.

CASES FROM THE LITERATURE

Case 1. (Balado and Morea, 1927)[4]

A 36 year old female para vii, gravida viii, was admitted to the hospital with severe paraplegia during the last month of her pregnancy. She reported that she had noted weakness in both lower limbs toward the end of six of her seven previous pregnancies. On four occasions this subsided immediately following delivery, but on the remaining two occasions the weakness persisted for one and five months, respectively. Before the patient's expected date of confinement she suffered from cardiac failure and died. Necropsy revealed an epidural angiolipoma in the midthoracic region. No mention was made of an associated vertebral lesion.

Case 2. (Delmas-Marsalet, 1941)[7]

A 26 year old female was admitted to the hospital because of pain in her upper limbs, particularly the right, and difficulty in walking. Eight years previously, at the end of the second month of her first pregnancy, she had experienced similar symptoms which progressed gradually until term. Immediately following delivery remarkable improvement was noted, leaving only slight difficulty in gait. Five years later, once again toward the end of the second month of pregnancy, she experienced radicular pain and paresis of the lower extremities which improved following delivery. Five months before admission, this time without pregnancy, the radicular pain became worse and was accompanied by electrical sensations passing down her back and spontaneous spasms in her legs. This did not regress as it had on the two previous occasions. Examination revealed a spastic paraparesis with hypalgesia up to the D-2 level.

Myelography revealed partial block with irregular vascular patterns between D-2 and D-5. Laminectomy disclosed an epidural hemangioma in this region. The lesion could not be removed surgically and radiation therapy was administered.

Case 3. (Guthkelch, 1948)[8]

A 34 year old female, para ii, gravida iii, was admitted to the hospital in the thirty-sixth week of pregnancy. Four weeks previously she had noted girdle pains around her lower chest. Two weeks later she experienced numbness and tingling in her lower extremities and a dribbling urinary incontinence. This progressed rapidly to spastic paraplegia. Laminectomy was performed and a vascular mass was encountered in the epidural space between D-4 and D-6 and could not be removed because of hemorrhage. The patient's condition worsened. She went into labor on the fourth postoperative day and was delivered spontaneously of a normal infant. The following day she developed acute gastric dilatation, went into collapse, and died within a few hours.

Necropsy confirmed the diagnosis of epidural hemangioma and also revealed a vertebral hemangioma involving the body of D-5. The latter had not been evident in the roentgenograms made at the time of admission.

Case 4. (Lam, Roulhac, and Erwin, 1951)[9]

A 36 year old negro female, para viii, gravida ix, was admitted to the hospital during the last month of her pregnancy. One month previously she first noted weakness and paraesthesias in both lower extremities. Subsequently she complained of thoracic backache and a girdle sensation around her upper abdomen. This progressed rapidly to a spastic paraplegia. There was no history of similar complications associated with any of her previous pregnancies.

She improved following delivery, but within a few weeks became slightly worse again. There was no roentgenographic evidence of abnormality in the films of the thoracic spine. Myelography demonstrated a block at the D-3 level.

Dorsal laminectomy disclosed a vascular epidural tumor which was diagnosed histologically as hemangioma.

Five months later the patient's recovery was complete.

DISCUSSION

Although reports of lesions of the kind described above in association with the pregnant state have been very infrequent, one suspects that this relationship may be more common. Three of the cases reported here were first diagnosed as multiple sclerosis because of the remitting course. Therefore, it seems quite possible that other patients diagnosed during pregnancy as having multiple sclerosis may well have had neurologic symptoms which improved or disappeared following parturition on the basis of some process other than demyelinating disease. Although one might consider this a rather rare occurrence, it would seem reasonable from the present evidence that the syndrome should be considered whenever paraplegia develops during pregnancy.

It is not always possible to identify the lesion by x-rays of the spine, since the vertebral column itself may not be involved and lesions in the epidural space alone cannot be identified by the ordinary roentgenographic examination. However, cerebrospinal fluid examination with manometric measurements should present evidence of spinal subarachnoid block and a myelogram should confirm the diagnosis. Where a vertebral lesion is evident by x-ray

examination, localization of the lesion is made with greater facility.

One of two possible mechanisms must be considered to be operative in the production of this syndrome: 1) increase in venous pressure resulting from mechanical obstruction by the pregnant uterus of the blood flow from the paravertebral veins into the inferior vena cava, or 2) the effects of the hormonal alterations associated with pregnancy on a pre-existing vascular lesion.

In all of the patients whose histories are presented here, with the exception of case 2, symptoms of an intraspinal lesion developed during the last half of the pregnancy. In case 2, however, the symptoms began at the end of the second month in each of two pregnancies.

In view of the fact that improvement in these patients has been noted during the immediate postpartum period, it would seem reasonable to assume that venous back pressure may play a definite role in producing cord compression. If it were not for the fact that case 2 developed symptoms before the pregnant uterus had reached a size where venous obstruction could be a determining factor, this would seem to be an acceptable explanation. However, it appears more reasonable to assume that endocrine factors are important.

Estrogen levels increase remarkably during pregnancy and fall abruptly following parturition. It has been suggested that they may even fall at the onset of labor and that a sudden decrease in estrogen level may be partially responsible for the initiation of labor. The rise in estrogen level is considered at least partially responsible for the retention of sodium and nitrogen resulting in increased intracellular fluid and an increase in intravascular fluid, as well. Estrogen levels which decline at the time of parturition will begin to rise once again when the normal menstrual cycle is reestablished. Ordinarily, in non-nursing mothers this may be expected to occur in from six to eight weeks following parturition. On the other hand, in nursing mothers this may not occur for many months. The fact that several of these patients have reported an exacerbation of symptoms weeks or months following delivery, even though they might not be pregnant at the time, may be accounted for in part at least by the reconstitution of the normal menstrual cycle. No information is available, unfortunately, in those cases reported previously as to whether the patients were nursing or not nursing their newborn infants.

The hormonal effect may be directly upon the endothelium of the vascular channels, but such a phenomenon has never been demonstrated. It would seem that a better explanation relates to the increased blood volume which may lead to distention of the vascular channels in these lesions. Vascular changes secondary to these endocrine influences may contribute to the symptoms of other hemangiomata during pregnancy. Rose[10] and Letterman and co-workers[11] have reported several cases of capillary hemangiomata which became enlarged during pregnancy and regressed during the puerperium. They have suggested that certain factors of etiologic significance, probably endocrine in nature, occurring during pregnancy, were responsible for these changes.

SUMMARY

1. Four cases of spinal epidural hemangioma producing spinal cord symptoms and signs, previously reported in the literature, have been reviewed. One additional case with an associated vertebral hemangioma is reported.

2. The relationship of the occurrence of symptoms to the pregnant state is considered, with regard to mechanical factors resulting in venous obstruction and to possible hormonal factors influencing the vascularity of the lesions.

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Significance of Oculocephalic and Caloric Responses in the Unconscious Patient

Morton Nathanson, M.D., Philip S. Bergman, M.D. and Paul J. Anderson, M.D

THE SIGNS commonly relied upon to establish the degree of unconsciousness are the responses to stimuli, including painful stimuli, corneal reflexes, pupillary reactions to light, and deep tendon reflexes. We have observed at times that these signs do not reflect the true degree of unconsciousness. The literature makes little reference to the oculocephalic reflex ("doll phenomenon") and the caloric test in relation to the state of consciousness or as a means of localizing lesions in comatose patients. The value of vestibular stimulation, particularly the caloric test, as a localizing tool in intracranial disorders has been reported extensively,[1–8] but no reference could be found which described the influence of the state of consciousness at the time of testing. Ford and Walsh[8] employed the oculocephalic reflex in their investigations, but here again the state of consciousness was not considered. Klingon in 1952[9] performed caloric tests in a comatose patient and observed disconjugate ocular responses similar to the pattern described with lesions of the median longitudinal fasciculus (abduction of the eye on the stimulated side, the opposite eye remaining in the midposition). Postmortem examination in this case revealed large demyelinating lesions in the tegmentum of the midbrain. A preliminary report by Bender, Bergman, and Nathanson in 1954[10] described oculocephalic and caloric responses in six comatose patients.

MATERIAL AND METHOD

Oculocephalic and cold caloric responses were studied in patients showing varying degrees of unconsciousness due to intracranial lesions and in normal subjects (patients without evidence by history or examination of central nervous system disease) under sleep induced with barbiturates. Of the patients with brain disease, only the verified cases are reported. There were 23 postmortem examinations and five cases of severe barbiturate poisoning.

The oculocephalic reflex was elicited by rapidly turning the head to the side and observing the associated ocular movements. Caloric stimulation consisted of a continuous stream of ice water into each ear, carried on for three minutes unless an ocular response was noted before then.

The normal oculocephalic response, described by Bielschowsky[11] and investigated further by Holmes,[12] consists of conjugate deviation of the eyes to the side opposite the direction toward which the head is turned, as if the eyes had been "left behind" by the turning head. Even when fixation of a target is not possible, as in total darkness or in sleep, rapid passive head turning produces similar ocular responses. The normal ocular response to cold caloric stimulation in the fully conscious patient is a jerky nystagmus, with the quick phase in the direction opposite to the side of stimulation. The subject is able to pursue a target in all directions and there is no involuntary tonic ocular deviation.

RESULTS

Normal subjects under induced sleep with barbiturates. The ocular response to cold calorics in induced deep sleep (barbiturates) in normal subjects was tonic conjugate deviation of the eyes to the side of stimulation, with or without nystagmus. Under these conditions (deep sleep) the oculocephalic reflex usually was absent. In lighter stages of induced sleep, caloric stimulation frequently caused arousal and a typical ocular response. The oculocephalic reflex was preserved and the barbiturate nystagmus became apparent with this maneuver.

Proved cases of brain disease including patients with severe barbiturate poisoning. 1) Patients who showed absent oculocephalic and caloric responses, that is, no ocular movements on passive head turning or on caloric stimulation, proved to have brainstem damage mostly involving the pons and/or midbrain. However, the four cases of severe barbiturate poisoning and the one case of massive subarachnoid hemorrhage also showed absent oculocephalic and caloric responses. 2) Of the six

From the department of neurology of Mount Sinai Hospital, New York City, the department of medicine (neurology section), Long Island Jewish Hospital, New Hyde Park, L. I., and New York University College of Medicine, III Division Neurology, Bellevue Hospital, New York City. Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 25, 1957.

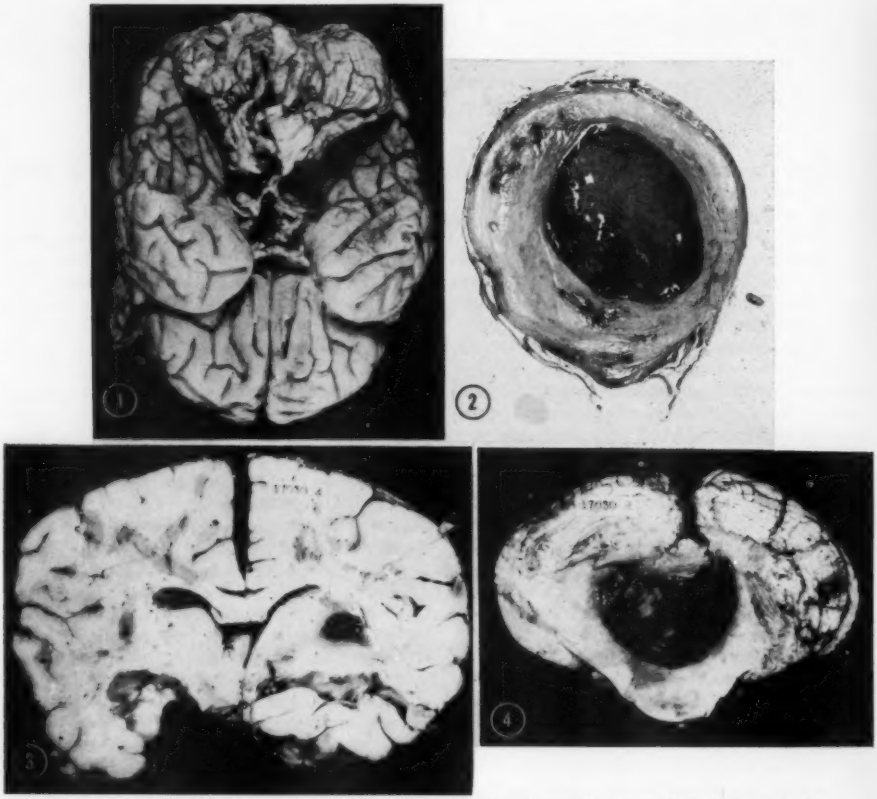
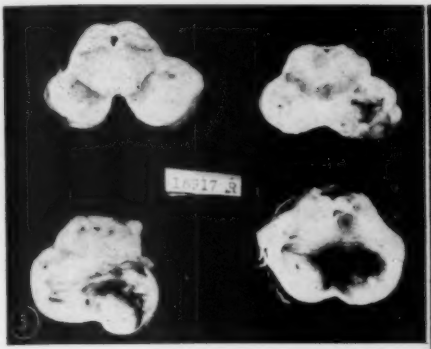


FIG. 1. Case of basilar artery occlusion. The entire midbrain "fell apart" as a result of extensive malacia. The cut basilar artery shows complete occlusion.
FIG. 2. Section of the basilar artery completely occluded by organized thrombus. Oculocephalic and caloric responses were absent.
FIG. 3. Tumor, glioblastoma, deep in the right cerebral hemisphere.
FIG. 4. Secondary severe brainstem hematoma, mainly of the pons. Where previously the oculocephalic and caloric responses were normal, no ocular response could be elicited by either of the tests when the patient became comatose.

patients who showed disconjugate ocular movements as a result of either one or both of these tests, four proved to have brainstem damage (table 1). 3) Patients who showed "intermediate" oculocephalic and caloric responses (combination of preserved oculocephalic reflex and tonic ocular deviation with or without nystagmus on caloric stimulation, or absent oculocephalic response with tonic ocular deviation on caloric stimulation, and so on) were considered to be in a "lighter" state of unconsciousness. Localization of pathology in this group was much less reliable, although most of the cases showing supratentorial pathology were in this category (table 2). The patients with barbiturate poisoning who had no oculocephalic or caloric responses on admission later showed "intermediate" reactions as the state of consciousness lightened. The responses became normal as consciousness returned. In other patients who showed initially "intermediate" responses and subsequently no reaction or disconjugate ocular movements by these tests, secondary brainstem damage was suspected. This was corroborated in two cases in which the autopsy revealed supratentorial lesions, with associated brainstem hemorrhage.

Other criteria for the evaluation of the depth of unconsciousness, such as the presence or absence of the corneal reflexes, pupillary light



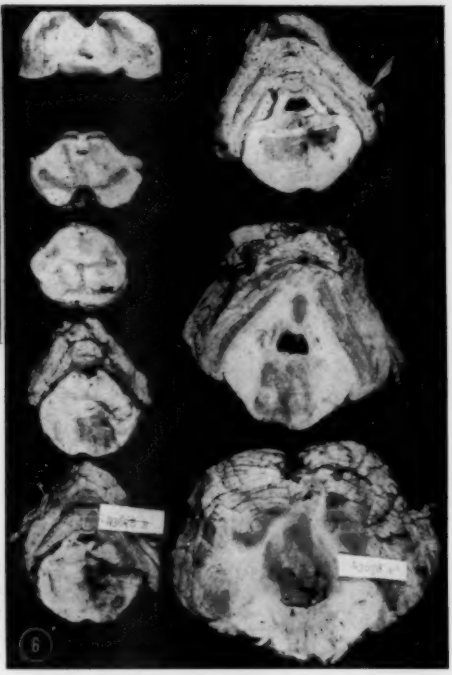


FIG. 5. Case of basilar artery occlusion showing hemorrhagic lesions of the right side of pons. Oculocephalic reflex was absent. Caloric stimulation of the left ear produced slight tonic deviation of the left eye only. Stimulation of the right ear elicited no response. FIG. 6. Case of basilar artery occlusion showing hemorrhagic lesions of the pons involving mostly the right side. Oculocephalic reflex was absent. Caloric stimulation of the right ear elicited disconjugate ocular deviation. Stimulation of the left ear produced conjugate deviation of the eyes to the left.

reaction, deep tendon reflexes, and response to noxious stimuli, also were recorded. It was found that these signs did not always correlate with the findings of the oculocephalic and caloric tests. In four patients who showed preserved corneal, pupillary, and deep tendon reflexes, caloric stimulation and oculocephalic reflexes were absent. This was the only clue that the patient was in a deeper state of unconsciousness than was suspected. The opposite was true in three other patients in this series, and the fact that tonic ocular deviation was elicited led us to believe that the patients were not in very deep coma. This was corroborated subsequently by return of consciousness.

In summary, we observed that the integrity of the oculocephalic and caloric reflexes depended mostly on the degree of unconsciousness. The changes in oculocephalic and caloric responses paralleled closely the degree of induced sleep in normal subjects. The absence of both reflexes was found in a high percentage of patients with proved brainstem damage, particularly of the pons and midbrain. How-

TABLE 1

A. *Proved cases showing absent oculocephalic and absent cold caloric responses*	
Brainstem lesions (Involving tegmentum and basis)	6*
Barbiturate poisoning	4
Massive subarachnoid hemorrhage (Clotted blood over cerebral convexities and base)	1
B. *Proved cases showing absent oculocephalic reflex and disconjugate ocular movements on cold caloric stimulation*	
Brainstem lesions	4
Tuberculous meningitis (Thick meningeal exudate about the base)	1
Barbiturate poisoning	1
C. *Proved cases showing disconjugate ocular movements with oculocephalic and cold caloric stimulation*	
Brainstem lesions	2
	19

*(5 basilar artery occlusion, 1 hemorrhage secondary to cerebral tumor)

TABLE 2

Proved cases showing "intermediate" responses to oculocephalic and cold caloric stimulations. (Absent or normal oculocephalic reflex and tonic conjugate ocular deviation with or without nystagmus on cold caloric stimulation)	
Encephalomalacia in the distribution of the right middle cerebral artery	1
Diffuse encephalopathy	4
Torulosis	1
Hemorrhage in the region of the posterior third ventricle	1
Metastatic lesions of the cerebrum	1
Craniopharyngioma	1
	9

ever, we hesitate to implicate this region as being solely responsible, since diffuse cerebral and brainstem dysfunction (barbiturate poisoning, massive subarachnoid hemorrhage) also obliterated these ocular reactions. Disconjugate eye movements elicited by either or both of these tests likewise correlated significantly with brainstem lesions. Oculocephalic and caloric examinations were found to be reliable indicators of the stage of coma and, when employed serially, were useful for prognosis. Frequently the tests had localizing value.

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■ The symptoms produced by tumour (of the spinal cord) vary greatly. Neuralgic pain in the back, over the seat of the tumour, appears to be an almost constant symptom. "Pain," says Dr. Reynolds, "is more marked in cases of carcinoma than of tubercle." If a particular nerve be irritated by the tumour, there may be pain, tingling, or some other anomalous sensation in the part or parts supplied by its sentient fibres, or some morbid form of contraction in the muscles supplied by its motor fibres. If a particular nerve be pressed upon more decidedly by the tumour, there may be local anaesthesia, or paralysis instead of morbid sensations or muscular contractions. It is but seldom, however, that these symptoms of irritation or pressure are so strictly localized; and in fact, the presence of the tumour is made known usually only by more general symptoms of irritation, or compression, or inflammation, which, instead of being in any way pathognomonic of tumour, may arise from many other causes. "There is, indeed," as Dr. Gull says, "no symptom, or single group of symptoms, which, taken alone, can serve as a secure basis for diagnosis."

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

Caloric Vestibular Reactions in Transtentorial Herniation of the Brainstem

Kjeld Vaernet, M.D.

IT IS WELL KNOWN that the severe symptoms in cases of transtentorial herniation, secondary to supratentorial space-taking lesions are caused by disturbances in brainstem function.[1–8]

The area of greatest direct strain to the brainstem structures is at the level of the inferior colliculi and the cerebral peduncle. An additional cause of neuronal dysfunction is interference, by the herniation, with the venous return from the brainstem.[9,10] This takes place mainly upward into the basal vein of Rosenthal and from there to the vein of Galen.[11,12] Doubtless, the arterial blood supply to the brainstem is also seriously disturbed in these cases.[13,14]

This results in the clinically well known syndrome of transtentorial herniation, characterized by a progressive clouding of consciousness, changes in the pulse rate and blood pressure, stiffness of the neck with extensor rigidity, and frequently a bilateral Babinski sign. In addition to this, the fixed dilated pupil is a common occurrence, unilateral at first, bilateral in the terminal stage.

In slowly progressive cases, one or more of these signs may be found over quite a long period of time, indicating a more or less severe dysfunction of the brainstem. In such cases disordered ocular movements should be expected, and this has indeed often been recorded in the nature of oculomotor and abducent nerve palsies,[15–18] whereas disorders of conjugate ocular movements referable to an indirect brainstem lesion are only recorded in cases of subtentorial masses.[19,20]

This would seem to imply that such disorders are a late occurrence in the syndrome of disordered brainstem function. In the later stages of transtentorial herniation, the accompanying unconsciousness will prevent testing of the ocular movements.

Recently, however, Klingon[21] succeeded in demonstrating disorders of the conjugate ocular movements in a comatose patient after cold caloric stimulation of the ear. His patient had a lesion of the brainstem involving the posterior longitudinal bundle bilaterally between the abducent and the oculomotor nuclei.

This localization would correspond to the area of the brainstem where damage is most likely to occur in cases of transtentorial herniation. Therefore, we made a study of the vestibulo-ocular reflexes, using ice-water irrigation of the ear, in 50 patients with supratentorial space-taking lesions.

The irrigation of the ears was carried out with 20 ml. of ice-water, with a temperature of 2° to 5° C. The patient was in a prone position with his head slightly elevated, so that the horizontal semicircular canal was affected primarily. The intervals between the conclusion of one test and the beginning of another was at least two minutes.

In 26 of the patients it was possible to demonstrate disorders in the pattern of the vestibulo-ocular reactions. One of these cases has recently been published by Ethelberg.[22]

In all cases of abnormal reaction the patient displayed symptoms of a disordered brainstem function, commonly denoted as signs of a transtentorial herniation of the midbrain. The severity of these signs and symptoms ranged from clouding of consciousness, accompanied by a drop in the pulse rate and commonly some stiffness of the neck, to a state of profound unconsciousness with a universal extensor rigidity and fixed dilated pupils.

The main pattern of the abnormal vestibulo-ocular reactions varied from a conjugate deviation of the eyes with a slight nystagmus, over a tonic conjugate deviation without nystagmus, to a condition best described as an internuclear paralysis: that is, a maximum abduction of one eye, while the other eye is not adducted beyond the midline. This latter reaction would seem to indicate a lesion of the fascicular connections between the abducent and the oculomotor nuclei.[23–25]

The abnormality of the vestibulo-ocular reflexes – in different patients and in the same patient at different times – was found to be roughly parallel to the clinical condition, abnormality progressing in the sequence mentioned with deterioration of the patient's vital signs secondary to the progression of the transtentorial herniation, and in the final stages with decerebrate rigidity the reactions were completely abolished.

From the state department of neurosurgery, City Hospital and University of Aarhus, Denmark.

A detailed analysis of this material will appear later, but a case history will serve to illustrate the reactions in a typical case.

CASE REPORT

A 43 year old man had had periodic attacks of headache accompanied by nausea and vomiting for about six months. For about two weeks he had experienced episodes of blurred vision, and for the last week he had been progressively somnolent.

On examination he was found markedly somnolent, but was able to cooperate to a certain extent. The eye movements and the pupillary reactions were normal. The pupils were equal in size. There was a slight blurring of the optic disks. The visual fields showed a doubtful upper left defect, but cooperation was too poor for proper evaluation. There was a left lower facial weakness but, as far as cooperation permitted, no paresis of the extremities could be disclosed. A universal hyporeflexia with a left-sided Babinski and a right extensor plantar response was found. The systolic blood pressure was 145 and the pulse rate about 80, occasionally dropping to 60. On otologic examination hearing was grossly normal and normal calorigrams were obtained bilaterally.

Ice-water irrigation of the ears was then performed, eliciting a normal nystagmus of 60 to 70 seconds duration.

A right-sided carotid angiogram revealed changes typical of a large temporal tumor, and a marked dislocation of the posterior cerebral artery into the tentorial aperture was seen.

During angiography the patient was restless, and the intravenous administration of 600 mg. of Pentothal was necessary to obtain satisfactory films. After the procedure the patient remained in a deep stupor for about six hours, reacting only slightly to painful stimuli. His blood pressure rose to about 170 and the pulse rate was 56 to 60. The eyes were slightly divergent, the pupils equal in size, rather small, with only a sluggish reaction to light.

While the patient was in this condition, about four hours after angiography (that is: at a time when the effects of Pentothal should be eliminated), the ice-water irrigation was repeated.

After irrigation of the right ear there was a latency period of 30 seconds, after which the right eye was maximally abducted and stayed immobile in abduction for 70 seconds. During this interval the left eye was adducted about 15°, but only for a few periods of three or four seconds each. Between these short periods of adduction the left eye stayed immobile in the midline. No nystagmus was observed. The abducted right eye went back to its original position slowly, and the eyes were again in slight divergence as before.

On irrigation of the left ear a latency period of 20 seconds was noted, after which the left eye moved into a maximally abducted position and stayed there for 40 seconds. It then slowly resumed its former near-midline position. During this the right eye never moved beyond the midline. There was no nystagmus in either eye.

At operation a large temporal astrycytoma, infiltrating deeply toward the basal ganglia, was removed. The postoperative course was uneventful.

On the fifth postoperative day he was still somewhat somnolent but cooperative. The eye movements were unlimited. A caloric test with ice-water was again performed, eliciting a normal nystagmus from both labyrinths.

COMMENT

To summarize the case under discussion, this was a patient with a supratentorial tumor, exhibiting clinical signs of increased intracranial pressure, but with normal responses to caloric vestibular stimulation. The development of a transtentorial herniation was assumed by clinical and assured by angiographic evidence. Caloric vestibular stimulation during this stage resulted in dissociated eye movements of the internuclear paralysis type.

For a probable explanation of the functional disorders of the vestibulo-ocular reflex mechanism recorded in this case, attention should be directed to some recent experimental observations upon the neurophysiologic basis of these reflexes. The present concept is based mainly on the fundamental analyses by Lorente de No[26,27] on the functional properties of the brainstem reticular systems.

The problem has been further elucidated by Szentágothai who, as a result of anatomic and experimental observations, maintains that the elementary reflex arc is set up by a simple three-neuron connection between the receptor elements of the crista ampullaris and the nuclei of the eye muscles. The internuclear pathways of the second neuron ascend within the posterior longitudinal bundle of the brainstem.

By utilizing the degeneration method he found[28] that each labyrinth has numerous direct three-neuron arcs with six of the 12 extraocular muscles: the ipsilateral medial rectus, superior rectus, and superior obliquus, as well as contralateral lateral rectus, inferior rectus, and inferior obliquus. With the remaining six muscles the same labyrinth has only very few three-neuron connections.

A more detailed analysis of these pathways has been made by the same author[29] who, in experiments with artificially induced currents of fluid in the isolated semicircular duct, found that each semicircular duct has a predominant functional connection with only two of the extraocular muscles. From the horizontal semicircular duct, which is the relevant one in this

discussion, the direct three-neuron connections were to the ipsilateral medial rectus and the contralateral lateral rectus.

Confirming the original views of Ewald,[30] it was further shown that a current in the appropriate direction, that is, for the horizontal duct a current directed toward the ampulla, would produce contractive responses in the two muscles with which there were direct three-neuron connections, while currents of the opposite direction would produce mainly inhibitory responses.

This was corroborated by Gernandt[31] who was able to pick up signals from a single neuronal unit in the vestibular nerve of the cat with a microelectrode. He found that stimulation with hot water caused excitation, while the response to cold water was an inhibition of neuronal activity.

That the internuclear connections ascend in the posterior longitudinal bundle has been established in a series of experiments[29] where a transsection of the pons was performed, leaving only the posterior longitudinal bundle intact. In these cases it was still possible to elicit the typical three-neuron responses and no other typical contractive responses could be obtained. In experiments with isolated transsection of the posterior longitudinal bundle, these basic contractive responses could no longer be evoked, while the inhibitory responses remained intact.

It follows from this that the inhibitory responses run mainly through the reticular formation, which also harbors multiple multineuronal chains connecting the vestibular nuclei with any set of the extraocular muscles.

The function of the multineuronal chains (in relation to the vestibulo-ocular reflexes) seems to be one of modification and integration, superimposed upon the direct vestibulo-ocular connections.[27] The intactness of the reticular formation is also a condition for the production of the quick component of the nystagmus,[26,32] which must probably be looked upon as a result of impulses set up by the vestibular activity in the closed circuits of the reticular formation and at a certain stage of excitation interrupting the direct motor discharges in the posterior longitudinal bundle.[27] This would account for the rhythmic character of the nystagmus.

The patient in the present case had typical signs of disordered brainstem function due to a transtentorial herniation. At this stage the formerly normal vestibulo-ocular reflexes had changed to a response characterized by movements of the eyes in the horizontal plane, with a maximum contraction of the ipsilateral lateral rectus, but no – or very slight – contraction of the contralateral medial rectus and without any nystagmus.

In the absence of signs of an oculomotor nerve paralysis, this would correspond neurophysiologically to a simple three-neuron reaction evoked by cold water application, creating an ampullofugal current in the horizontal semicircular canal, but with an interruption of the fascicular connections in the posterior longitudinal bundle between the abducent and the oculomotor nuclei, allowing only the action of the lateral rectus to appear. The tonic monophasic character of the reaction and the absence of nystactic movements would seem to indicate that the transmission through the neuronal elements of the reticular formation was also impaired.

This type of reaction is similar to the disorders of conjugate ocular movements described as anterior internuclear paralysis[23,24] (the prefix "anterior" being irrelevant, as pointed out by Cogan[33]) or the syndrome of the posterior longitudinal fasciculus.[34]

The lesions of the brainstem which occur during transtentorial herniation are the result of complex pathogenetic factors involving both direct mechanical strain to the structures affected and indirect damage by interference with their arterial and venous circulation. Therefore, it is hardly surprising that disturbances in the vestibulo-ocular reflexes may follow a more complicated pattern than in the case recorded here. For instance, a train of varying and complex reactions to caloric stimulation during transtentorial herniation of the brainstem secondary to a supratentorial tumor is seen in the case published by Ethelberg.[22]

As pointed out by Jefferson[8] and Munro and Sisson,[35] among many others, it is important to recognize impending disaster in these patients if surgical intervention might correct the situation.

From the observations of Bender and Weinstein,[25] it is evident that slight or latent disturbances in the vestibulo-ocular connections are augmented and readily demonstrated during vestibular stimulation.

The caloric vestibular test might be an additional help in some of these cases in recognizing the existence of a functional disturbance in the neuronal transmission at the pontomesencephalic level of the brainstem, before these functional changes have progressed to irreparable anatomic damage.

Irrigation of the ear with 20 ml. of ice-water seems to be a simple and effective method of testing the vestibulo-ocular reflexes.

SUMMARY

In patients with signs and symptoms of a transtentorial herniation of the brainstem secondary to supratentorial tumors, caloric vestibular stimulation may disclose abnormalities in the vestibulo-ocular reflexes, indicating a disturbance of the neuronal transmission in the brainstem.

The nature of these disturbances and the probable localization of the lesions are discussed in the light of a case history, with reference to recent neurophysiologic experiments.

It is suggested that the caloric vestibular test, performed with 20 ml. of ice-water, might be an additional help in some of these cases as a simple method for objective recognition of the neuronal dysfunction in the brainstem.

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Rehabilitaton of the Aphasic Patient

A Survey of Three Years' Experience in a Rehabilitation Setting

Morton Marks, M.D., Martha Taylor, M.A. and Howard A. Rusk, M.D.

THE PATIENT with aphasia presents one of the most complex yet interesting problems the neurologist encounters. Although the literature pertaining to aphasia has attained voluminous proportions, the primary emphasis has been directed toward the pathogenesis, clinical features, classifications, and theoretical implications of the functional capacities and their localization within the human brain. The considerable numbers of aphasic patients produced by the ravages of the two world wars stimulated exploration of the retraining potential of this group. The details of many comprehensive programs have been described. However, the majority of these patients had sustained their aphasia as the result of trauma.[1–3] Comparable extensive studies of the reeducation experiences of patients with aphasia secondary to disease, as commonly encountered in the civilian population, are lacking. The few that have been attempted are of such limited numbers of patients as to be of questionable scientific and statistical significance.

Concomitant with the rather recent emphasis on rehabilitation, greater numbers of the latter type of patient have been referred for reeducation and studied intensively. This paper is an attempt to evaluate the results critically and to describe the factors encountered when the facilities of the rehabilitation center are utilized in attempting reeducation of the patient with aphasia, as commonly encountered in medical practice.

CASE MATERIAL AND PROCEDURES

A series of 324 patients evaluated and/or treated during the preceding three-year period in the speech department of the Institute of Physical Medicine and Rehabilitation, New York University-Bellevue Medical Center comprise the basis for this study. All of the patients were considered to have had some form of speech disturbance associated with organic brain damage, who premorbidly were considered to have had "normal" language function.

Referral sources included private physicians, welfare agencies, private speech therapists, other hospitals, and families of aphasic patients. The patients were referred to the speech department only after a comprehensive medical review to ascertain whether or not further definitive medical care was indicated. Most of the patients were admitted for a total rehabilitation evaluation, but occasionally patients were admitted only for speech evaluation and treatment.

The speech evaluation included a psychological work-up, pure tone audiometric sweep testing, Halstead-Wepman aphasia screening test, a family interview, a patient interview in the presence of the family, a patient interview without the family present, and an evaluation of functional ability, that is, language abilities pertaining to daily living, such as telephoning, writing his name, and so on.

The diagnostic classification included:

1. Predominantly expressive type aphasia, in which the greatest difficulty exists in the expressive areas of language and might include part or all of the modalities of communication.
2. Mixed or expressive-receptive type aphasia, in which there seemed to be equal involvement of both expressive and receptive functions of language.
3. Predominantly receptive type aphasia, in which the primary difficulty appeared to be in comprehension.
4. Global aphasia, in which there appeared to be no language capacity in the expressive or receptive areas of communication.[3]

The functional classification included:

1. Vocational adequacy in language. These patients were considered adequate enough to qualify for vocational placement, although not necessarily in their former vocation.
2. Home adequacy in language. These patients were considered adequate for functioning at home, that is, they are able to make their daily wants known and must have sufficient receptive ability to manage the phone, read, understand signs, and so on.
3. Rehabilitation center adequacy in language. The patient is considered able to follow a program.

From the departments of neurology and physical medicine and rehabilitation, New York University College of Medicine, New York City.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 27, 1957.

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TABLE 1

	Total Aphasics	Expres.	Recept.	Exp.-Rec.	Global	Dysarthria	None	Unknown
Male	136 (62.1%)	94	7	27	8	65 (29.6%)	18 (8.2%)	3
Female	69 (62.7%)	53	1	12	3	32 (29.1%)	9 (8.2%)	1
Totals	205 (62.4%)	147	8	39	11	97 (29.4%)	27 (8.2%)	4
% Aphasics		(71.7%)	(3.9%)	(19.0%)	(5.4%)			

He has adequate comprehension to allow him to attend group and individual classes. He can use the elevator without assistance, and can follow nurses' and therapists' instructions.

4. Institutional adequacy in communication. The patient is unable to perform in any of the higher level functional activities.

The evaluation findings were presented to the medical resident in charge of the patient and presented at the time of the staff evaluation of the patient. The decision as to whether or not to undertake language retraining usually reflected the combined opinions of the resident, the physician in charge, and the speech pathologist, and were frequently influenced by the neurologic and psychologic problems uncovered. The actual technics and type of retraining to be utilized were usually determined by the speech pathologist. Although theoretically the evaluation process was accomplished in one session, in actuality the evaluation process was most commonly performed concurrently as part of a trial period of therapy. An attempt at the prognosis was made during the evaluation; however, it was recognized that this was primarily a subjective assessment of the patient's potential and its confirmation depended upon a trial period of therapy.

The diagnostic and sex distributions are tabulated in table 1.

It should be noted that the numbers of patients recorded totaled 333. This is explained by the fact that nine aphasic patients were also considered to be dysarthric and classified in both groups (eight expressive and one receptive). The preponderance of men over women in this series was not considered significant, as this was approximately the ratio of admissions to the service during the period of study.

Disease processes, primarily cerebrovascular accidents, were considered to be the underlying cause in 93.6 per cent of the cases (table 2).

TABLE 2

Cause	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
Trauma	13(6.4%)	10	1	2	0
Disease	190(93.6%)	137	6	37	10

Table 3 records the age distribution. The incidence was noted to be highest after 50 years.

Vocational and educational surveys showed wide scattering of the patient population and were not considered significant (table 4).

The known educational backgrounds were widely scattered (table 5).

Handedness is recorded in table 6. It must be borne in mind that handedness does not unequivocally imply language laterality in the contralateral hemisphere.[5] In this series laterality was determined by asking the patient or family which hand the patient commonly used for performing normal functional activities.[7] It was recognized that writing was the result often of a specialized training technic and not an absolute indicator of handedness. The true incidence of left handedness among the general population is unknown. Most estimates are in the region of 5 per cent, with surveys reporting a decreasing frequency of left handedness with increasing age.[4]

The commonly associated physical disabilities are tabulated in table 7.

Detailed case studies, relating handedness and inferred language laterality, physical disability, and aphasia have been recorded by numerous authors. The accumulated studies, as do our findings, tend to corroborate Goodglass and Quadfasel's conclusions that cerebral laterality for language and handedness are not directly linked, and one does not determine the other.[5] The present series includes cases of aphasia in right handed individuals who had right cerebral involvement, left handers with left cerebral involvement, and left handers with right cerebral involvement. Although their incidence was small, these occurrences add

TABLE 3

Age	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
Under 30	14(6.9%)	13	0	1	0
30 to 40	16(7.9%)	14	0	1	1
41 to 50	43(21.2%)	33	3	7	0
51 to 60	68(33.7%)	50	0	15	3
Over 60	61(30.2%)	34	5	17	7

TABLE 4

Total Aphasics	Vocation
37	Professional
15	Semiprofessional
22	Owner, executive, large business
19	Small business owner
24	White collar worker
12	Skilled laborer
12	Unskilled laborer
42	Housewife
4	Student
18	Unclassified

TABLE 5

Total Aphasics	Education
38	Unknown
21	Under 6 years
12	6 to 7 years
11	8 years (grad.)
7	9 to 11 years
68	12 years (grad.)
16	13 to 15 years
87	16 years

evidence to that previously accumulated, which questions the validity of the concept of strict localization of cerebral functional capacities.

The duration of aphasia prior to the patient's evaluation are shown in table 8.

It should be noted that 50 per cent of the cases sought therapy or were appraised six months or more after the onset of symptoms. Only 27.8 per cent of the total were seen within three months after onset. This is of special interest in view of the fact that the period of spontaneous restitution of function is usually considered to be less than six months after the onset of illness. Expressive aphasics as a group sought therapy later than those with receptive components.

Few of the patients had had previous speech therapy; 81 per cent had had no therapy, 7.5 per cent had therapy of less than three months, and 11.5 per cent had had therapy of more than three months duration (table 9).

Most patients preferred outpatient status (62.5 per cent) (table 10). A higher percentage of the more severely involved aphasics sought inpatient care. Whereas 29.9 per cent of the expressive aphasics were inpatients, 33 out of 58 (56.9 per cent) of aphasics in other categories were inpatients.

The number of therapy sessions varied from none to more than 110. The scatter is evidenced in table 11. Forty patients (20 per cent) had no therapy. Only 79 (39.5 per cent) had more than 21 therapy sessions.

The duration of therapy, too, varied widely (table 12).

After discharge from the institute many patients were referred for further programs.

TABLE 6

Handedness	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
Right	196 (97%)	141	8	37	10
Left	6 (3%)	4	0	1	1

The type of program the patient actually carried out was decided through a recheck or by telephone contact with the patient one month after discharge to determine whether or not he had continued with the recommendations (table 13); 48.5 per cent of the patients continued with some form of program, usually a home program.

The treatment program was generally set up as follows. Individual sessions were limited to one-half hour per session. They were held in quiet, private quarters where there was a minimum of distraction. Attempts were made to offer the aphasic patient therapy early in the day before he fatigued. The equipment used included numerous objects – object pictures, object flashcards, phrase flashcards, sentence flashcards, blackboard and audiovisual devices. The latter included a large toy clock with moveable hands, a tape recorder for advanced patients, adult education grammar education reading material for advanced patients, block letters, word lists, materials from the aphasia manual,[8] the "Language Master" – an audiovisual device capable of reproducing specific structured visual material like nouns, phrases, sentences in auditory form through ear phones or in a free field through a speaker – and occasionally a mirror for patients with verbal aphasia.

Many technics of actual therapy were employed, such as matching of pictures, objects, and words. Naming was attempted through repetition, imitation, copying writing, dictation, and stimulation of the patient's identification. Calculations were performed using flashcards, quantities of similar objects, play-

TABLE 7

Physical Disability	Total Aphasia	Exp.	Rec.	Exp.-Rec.	Global
Right hemiplegia	183(90.6%)	132	8	35	8
Left hemiplegia	7(3.5%)	4	0	2	1
Ataxia	4(2.0%)	2	0	1	1
None	8(4.0%)	7	0	0	1

TABLE 8

Duration of Symptoms	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
Less than 1 mo.	9	8	0	1	0
1 to 2 mo.	25	19	0	4	2
2 to 3 mo.	23	13	3	3	4
3 to 4 mo.	14	11	0	3	0
4 to 6 mo.	31	18	0	13	0
6 to 9 mo.	23	13	1	8	1
9 to 12 mo.	15	11	1	2	1
1 to 2 years	23	19	0	3	1
Over 2 years	41	35	3	2	1

TABLE 9

Previous Speech	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
None	162	118	3	30	9
Less than 2 wk.	1	0	0	1	0
2 to 4 wk.	1	1	0	0	0
1 to 2 mo.	7	4	1	1	1
2 to 3 mo.	6	3	1	2	0
More than 3 mo.	23	18	0	4	1

TABLE 10

Status	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
In	77	44	3	22	8
Out	128	103	3	17	3

ing number games, and so on. Reading was attempted by first using flashcards with nouns and later using simple adult education readers. Writing was performed by first tracing and using block letters, and finally by writing from dictation. Conversation was utilized extensively to enhance the functional carry-over of the learned material. Auditory stimulation was offered to the patient in large amounts to stimulate speech production. Finally, functional technics like using the telephone in a controlled clinical setting, writing letters to friends, and ordering from actual menus, were employed.

Evaluation and measurement of progress were based almost entirely on the patient's increased functional ability. In the case of a patient who had a long term of therapy, the original Halstead-Wepman form was readministered. The patient's own expressions were frequently used as indicators of his progress.

Treatment was terminated when it was considered that the patient had reached his maximum level of language functioning; usually this was the combined opinion of the physician in charge and the speech pathologist that the patient had reached his maximal language capacity. Other causes for termination of therapy included disinterest of the patient in continuing therapy or the unfortunate inability of the patient to further finance speech therapy.

In most instances a home program was given to the patient at the time of discharge, even when it was believed that he had attained his maximal language level, as a supportive therapeutic measure; in addition, there was always the possibility he might increase his functional language ability.

Attempts at evaluation of treatment results are obviously difficult. Our criteria of classification were defined as follows:

Excellent: 1. Patient moved from one functional level to another during treatment. 2. Patient moved from one diagnostic level to another. 3. Patient acquired such a significant amount of increased language skill that, although he remained in one classification, he was judged to have made marked functional changes.

Good: Patient moved from either one functional level or one diagnostic level to another.

Fair: Patient did not move from one functional category to another, either functionally or diagnostically, but did make some functional gains within the original categories.

Poor: Patient exhibited no changes during treatment in functional language ability.

Evaluations were performed by three speech therapists. In all cases, for classification, two out of the three had to share the same opinion.

DISCUSSION

Opinion as to the functional value of a rehabilitation program for the aphasic varies.

TABLE 11

Sessions	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
None	40(20.0%)	28	1	9	2
1 to 10	50(25.0%)	36	3	8	3
11 to 20	31(15.5%)	25	0	5	1
21 to 30	25(12.5%)	15	2	6	2
31 to 60	28(14.0%)	18	2	5	3
60 to 90	12(6.0%)	8	0	4	0
91 to 110	2(1.0%)	2	0	0	0
More than 110	12(6.0%)	11	0	1	0

TABLE 12

Duration of Therapy	Total Aphasics	Exp.	Rec.	Exp.-Rec.	Global
None	40(20.2%)	28	1	9	2
Less than 1 mo.	51(25.8%)	33	2	11	5
1 to 2 mo.	43(21.7%)	28	2	10	3
2 to 3 mo.	26(13.1%)	20	2	3	1
3 to 6 mo.	24(12.1%)	20	0	4	0
6 to 9 mo.	10(5.0%)	8	1	1	0
9 to 12 mo.	2(1.0%)	2	0	0	0
More than 1 year	2(1.0%)	2	0	0	0

Many believe that the program itself has no significant influence on the rate of improvement, but rather consider improvement to represent spontaneous restitution or reorganization of the residual cerebral functional capacities. Others, including Goldstein,[1] Butfield and Zangwill,[6] and Weisenberg and McBride,[2] believe that retraining procedures may initiate or increase appreciably the rate of improvement.

Although theoretically feasible, when objective studies are undertaken in an attempt to clarify the problem, many difficulties become apparent. Controlled long-term studies utilizing comparable groups, one given and the other not exposed to therapy, are lacking. In addition, there are no clearly formulated criteria of what constitutes the "normal" spontaneous restitution of function following aphasia, or beyond what period of time spontaneous restitution of function cannot occur. Moreover, there is no uniformity or standardization of the materials or the procedures to be followed in retraining the aphasic or even unanimity of the implied underlying philosophy. Many attempts at speech retraining are based primarily on a phonetic and mechanical approach. Others attempt to have the patient relearn speech patterns utilizing successively more complex Gestalt conceptualizations.

One formidable aspect of the problem is that no universally accepted and standardized testing procedure exists, with which the degree of functional deficit and the extent or rate of subsequent improvement or return of function can be accurately graded and classified. The technic of using the pre-existing and subsequent functional capabilities (for example, school grade levels, used comparatively in evaluation of those cases who sustained their injuries during military service[3]) can only rarely be utilized for the patient encountered in civilian life.

Another important, and at times overlooked factor, is the unique psychologic status of each aphasic patient. Because of the communication difficulty, the usual psychologic and psychometric testing technics prove inadequate. The correlated problem of the patient's motivation and the important role the speech therapist may play in developing it are well recognized but have not as yet been clearly formulated or controlled in any appraisal of the effects of therapy.

In view of these difficulties, it is not suprising that the clinician varies in his concept of the management of and value of a speech program for the aphasic patient, ranging from an attitude of unbridled enthusiasm to, in many instances, one of therapeutic nihilism.

The results of the rehabilitation program are tabulated in table 14. The results obtained, although not as favorable as those reported by others whose aphasic patients were primarily the result of trauma, appear to be significant and suggest that a reeducation regimen is warranted for the aphasic, even the one of long standing. The best results were observed in the expressive aphasic patient.

A study of the individual cases revealed many additional interesting facts. Although treatment results appeared to be better in the younger groups, age alone did not preclude favorable results.

A relatively long duration of symptoms does not mitigate against successful therapy, although favorable results seemed to be more common if therapy was instituted earlier. One of the markedly expressive aphasic patients, a 37 year old man, made only slight functional improvement during the first year of his reeducation program, although therapy, which consisted primarily of a comprehensive home program with frequent checkups, was instituted within one month of the onset of his illness. He gradually started to improve and continued to do so over the following two-year period to the point of virtual recovery. He has returned to his occupation as a research chemist with a large organization, in charge of a department, capable of carrying out all required activities including lecturing. Another patient, a 46 year old woman who had failed to show significant gains during her first year of therapy, returned to such a high level of functional activity within three years from the onset of her acute symptomatology that she was considered to be one of our most

TABLE 13

Type Therapy Continued	*Total Aphasics*	*Exp.*	*Rec.*	*Exp.-Rec.*	*Global*
None	102(51.5%)	68	4	25	5
Home	60(30.3%)	46	3	8	3
Clinic	5(2.5%)	2	0	3	0
Prof.	31(15.7%)	25	1	2	3

TABLE 14

Results	*Total Aphasics*	*Exp.*	*Rec.*	*Exp.-Rec.*	*Global*
Excellent	11(6.9%)	9	1	1	0
Good	35(22.0%)	32	0	2	1
Fair	34(21.4%)	25	1	6	2
Poor	79(49.7%)	49	4	21	5

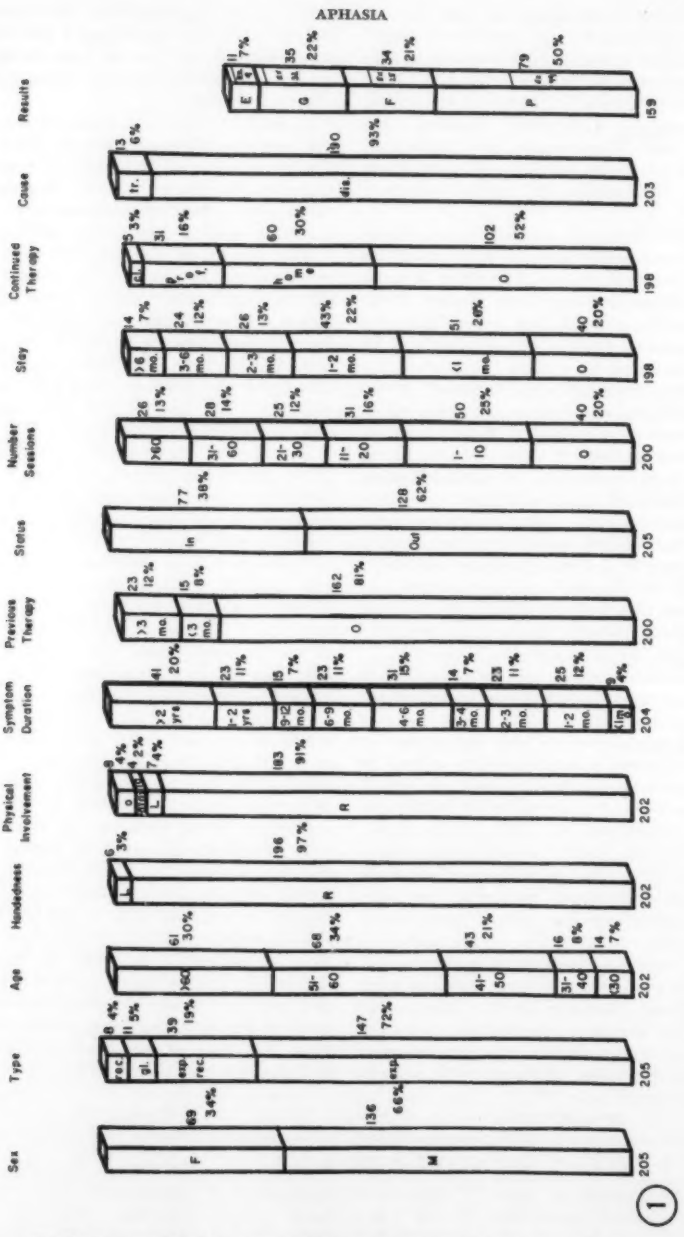

FIG. 1. Summary of data in a group of 205 aphasic patients evaluated and treated in a speech rehabilitation study.

successful results. We have learned that even small gains, if sustained, may warrant additional training.

One of our impressions, although as yet unproved, must be recorded. It was our feeling that those patients whose personality structure was and had been a relatively rigid one with compulsive features tended to do less well therapeutically than other patients whose personality had been considered premorbidly to be less restrictive. Further studies in this sphere are contemplated.

It must be noted, too, that our treatment facilities were encompassed in a comprehensive rehabilitation setting in which the emphasis was placed on retraining and rehabilitation of the "total" patient. The process of reeducating the aphasic patient was directed not only at the speech disability, but rather required consideration of the total language or communication disturbances. This then was combined in many instances with a comprehensive physical program.

Our results as recorded seem to warrant the extension of services to a large number of aphasic patients encountered in ordinary practice, despite the handicaps of age, disease, and relatively long duration of symptoms. They seem to suggest that a comprehensive rehabilitation regimen can significantly influence the functional capabilities of many patients with aphasia beyond the period when spontaneous improvement is to be anticipated.

SUMMARY AND CONCLUSIONS

Two hundred and five aphasic patients who had been evaluated and/or treated in the speech department of the Institute of Physical Medicine and Rehabilitation comprise the basis for this study. Only a small percentage of these were traumatically incurred aphasias. In all cases, aphasia as a diagnostic term is used to describe patients with language disturbances who premorbidly had normal language. The age range of the cases varied from three to 80 years of age. Such factors as vocational status, education, handedness, physical disability, previous speech therapy, number of therapeutic sessions, length of therapy, time lapsed before coming to the institute, rated degree of recovery, type of continued therapy, and cause of aphasia are data included in the statistical survey and summarized in figure 1.

The results seem to indicate that a comprehensive language retraining program will often prove to be of significant functional value to the patient, especially the one with a predominantly expressive type of aphasia, even beyond the period when spontaneous improvement is to be anticipated. Therapeutic nihilism on the part of the physician, family, or patient himself may well be a disservice to the patient. The therapeutic goals must be realistic ones, however, and subject to frequent review.

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ADDENDUM

Since publication of the paper "Cranial Bruit Associated with Occlusion of the Internal Carotid Artery" by Miller Fisher, M.D. (Neurology 7:299, 1957), the author's attention has been drawn to an earlier article by Dr. Henry Dunning ("Detection of Occlusion of the Internal Carotid Artery by Pharyngeal Palpation," J.A.M.A. 152:321, 1953), in which an ocular bruit was noted in two cases of carotid obstruction, and the idea hinted that the bruit might be a new sign of carotid disease. In fairness to Dr. Dunning, Dr. Fisher desires that this omission from the paper be corrected.

Postirradiation Cervical Myelopathy

Report of Two Cases

Hideo H. Itabashi, M.D., Jose Bebin, M.D., Ph.D. and Russell N. DeJong, M.D.*

RELATIVELY FEW CASES of injury to the cervical spinal cord secondary to irradiation have been reported in the literature. The hazards of intensive radiation therapy of diseases in the vicinity of the spinal cord and brain have been known for some time,[1,2] however, and it is probable that nervous system damage occurs more frequently than the literature suggests. Where a biopsied neoplasm is the target of irradiation, central nervous system signs which may appear later are usually attributed to either metastasis or extension of the lesion, especially when the neurologic disturbances develop after a period of apparent improvement. An error in diagnosis may be made if the possibility of radiation injury is not borne in mind.

BRIEF REVIEW OF THE LITERATURE

Many studies have been made dealing with the effects of radiation on the normal spinal cord of experimental animals[3–5] and upon the human spinal cord after a course of radiation for the treatment of spinal cord tumors.[6,7] Other reports have described the effects of radiation on the brains of experimental animals[4,8–12] and those of coincidental irradiation of the brain in the treatment of cerebral neoplasms or more superficial conditions.[13–22] Ahlbom, in 1941, first described spinal complications following radiation therapy of neoplasms outside of the spinal cord, and reported four patients out of 235 treated for hypopharyngeal neoplasms who later developed a progressive neurologic syndrome attributed to radiation injury of the spinal cord which terminated fatally.[23] Smithers and co-workers, in 1943, reported one patient out of 54 treated for cancer of the esophagus who later developed a spinal cord lesion at the level of irradiation.[24] Although Ahlbom gave a brief pathologic report of the spinal cord findings in his cases, he did not, as he intended, publish them in detail at a later date. Stevenson and Eckhardt, in 1945, presented the first detailed clinical and pathologic report.[25] In 1948 Boden described 10 cases of radiation myelitis in a review of 161 patients treated for various neoplasms in the vicinity of the cervical spinal cord.[2] Five patients had died, one was living with progressive signs, and four had "transient" symptoms without neurologic signs; postmortem examination was obtained in only two cases, in neither of which neoplasm was found. In 1950 Boden added three more cases in his paper covering radiation damage to the brainstem.[15] All three patients were living at intervals of 30, 32, and 84 months after the onset of neurologic symptoms, but two had definite neurologic residuals. Malamud and co-workers, in 1954, documented a case with autopsy findings.[26] There are undoubtedly other cases which were recognized and unreported. On the other hand, other cases which had radiation damage have gone unrecognized because of incorrect inference as to the etiology of the patient's symptomatology. Those cases with autopsy confirmation which have been reported in the literature are listed in table 1.

CASE REPORTS

Case 1. A 72 year old white man with a lymphoepithelioma of the left base of the tongue with extension to the left neck had 10,484 air roentgens directed at the tumor over 27 days. Fifteen months later he developed neurologic symptoms which progressed to a Brown-Séquard syndrome, then quadriplegia, and death ten months after onset.

A 72 year old retired university professor was in good health until the latter part of 1953 when he developed a sore throat and swelling in the left side of the neck and left base of the tongue. Examination showed a mass 3.0 by 3.3 by 1.0 cm. in size, situated 2.5 cm. below the angle of the mandible and anterior to the sternocleidomastoid muscle, and a mass 2.0 by 3.0 by 1.0 cm. in size at the base of the tongue on the left. On January 19, 1954 a biopsy was performed, and a pathologic diagnosis of lymphoepithelioma (transitional cell carcinoma) was made. From January 21, 1954 to February 17, 1954 he was treated with radiation therapy, receiving 93 roentgens (measured in air without back scatter) to each field at 250 KV (HVL 3.0 mm. cu.) daily over 27 days, with a total of 2,621 roentgens to each field of 6x16 cm. (direct-lateral, contralateral, anterior-posterior, and posterior-anterior). The total estimated dose was 10,484 air roentgens. The patient was then well

From the departments of neurology and neuropathology, University Hospital, Ann Arbor, Michigan.
Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 26, 1957.
*Present address: Henry Ford Hospital, Detroit, Michigan.

until June 1955, when he noted dragging of the feet, especially the left, and loss of sensation in the right leg. He also noted difficulty in use of the left hand, two painless blisters on the right foot, and a sharp pain in the neck with exertion.

Examination on June 21, 1955 showed scarring and pigmentation on the left side of the neck. No lymph nodes were palpable in the neck. There was tenderness on percussion over the spinous processes of C_4 and C_5. There was a partial Horner's syndrome on the left, with miosis and a narrowed palpebral fissure. There appeared to be some weakness of the lower portion of the face on the left, but this was felt to be secondary to scarring from radiation therapy. The gait was stooped and shuffling, and there was dragging of the left foot and some clumsiness of movements of the right foot. Muscle strength was diminished in the left upper and lower extremities, predominantly in the leg. Superficial pain sensation was absent on the right to the level of T_2 and pain and temperature sensations were diminished to the level of C_6 or C_5. Light touch sensation was normal. Vibratory sense was impaired bilaterally to the xiphoid process. Position sense was also impaired bilaterally in the lower extremities. Deep pain was absent in the right ankle. The deep reflexes were hyperactive bilaterally, more so on the left. There was a Hoffmann sign on the left and there were bilateral Babinski signs.

Roentgen examination of the spine showed extensive hypertrophic arthritis, particularly around the anterior margins of the bodies of the fifth to seventh cervical vertebrae, but no evidence of bone destruction. Chest roentgenograms showed only senescent changes of the thoracic aorta. Spinal puncture was performed, and there was no evidence of block. The fluid was clear and colorless and the pressure was normal. The spinal fluid protein was 24 mg. per 100 cc., and the colloidal gold curve was 0000000000. Myelography revealed good filling of the cervical subarachnoid space, except for a small horizontal defect in the midcervical area thought to be due to hypertrophic lipping.

When the patient was examined on October 3, 1955, there had been a definite progression of symptoms. Three to four weeks previously he had noted numbness and tingling beginning in the tips of the fingers on the left, which had progressed to involve the entire hand and arm. There had also been progressive weakness of the left hand and arm and dysesthesia, particularly to metal objects and also to light touch, of the left arm and hand. In addition, he complained of a dull aching pain in the suboccipital region and generalized fatiguability and weakness. On examination several subcutaneous nodules were palpated deep in the left side of the neck. There was slight swelling of the left wrist and hand with trophic changes of the skin of both legs. Motor examination showed marked flaccid weakness of the left upper extremity, moderate spastic weakness of the left leg, and slight weakness of the right upper extremity. No fasciculations were noted. There was absence of pain and temperature sensations on the right side to the level of C_6. Light touch was diminished in the left arm and lower extremity. Position sense was diminished in the left arm and hand. Vibratory sense was absent on the left side up to the clavicle and absent on the right to the iliac crest. There was complete stereoanesthesia of the left upper extremity. The patient stood with a stooped posture, walked with little or no associated movements of the left arm, and dragged the left foot. The deep reflexes were generally hyperactive, and there was a Hoffmann sign on the left with bilateral Babinski signs. Cervical spine roentgenograms showed no evidence of pathologic changes other than hypertrophic arthritis. The patient was placed on cervical traction for his pain, and then discharged with instructions in range of motion exercises.

Following this there was progressive disability. In November he was not able to stand alone or walk without assistance. His entire left side became almost useless. His right side remained quite strong, however, in spite of the fact that he was aware of loss of pain and temperature sensations on that side. He was able to write fairly well with his right hand. Examination on December 2, 1955 showed little voluntary movement of the left upper extremity and the hand on that side was edematous. There was complete stereoanesthesia of the hand, absence of vibration and position senses, and anosognosia as well. The patient frequently "lost" the hand and was unable to locate it. His left lower extremity was extremely spastic. There were hyperactive reflexes of both the upper and lower extremities on the left, and also, but to lesser extent, on the right. There was more weakness of the right leg than had been noted previously. Sensory examination showed a complete loss of pain and temperature sensation on the entire right side of the body to the third cervical segment. He was able to feel tactile sensation over the abdomen, thorax, and arm on the right, but he had marked impairment of this modality over the lower extremity on that side. Vibratory and position sensations were diminished in the right lower extremity, but normal in the right upper extremity. There was a band of loss of superficial pain sensation on the left side, extending from the third thoracic to the third cervical segment, with complete absence of superficial pain sensation in the sixth and seventh cervical dermatomes. The patient was also developing constipation and was noticing urgency and precipitancy of urination.

On March 19, 1956 the patient was readmitted to the University Hospital because of acute urinary retention. He was completely paralyzed in all extremities. He was even reluctant to move his head. There was fullness of the left supraclavicular fossa, with firmness to touch but no definite mass. He resisted movements of the head

TABLE 1

SUMMARY OF AUTOPSIED CASES OF POST-IRRADIATION CERVICAL MYELOPATHY

Case No.	Author	Age and Sex	Diagnosis	Field	Total r (air)	Duration of treatment (days)	"Free" interval (months)	Clinical findings	Pathology
1	Stevenson and Eckhardt, 1945	43M	Lymphoepithelioma nasopharynx	Intraoral 2.5 cm. diam., rt. temporal 6.0, lt. temporal 6.0, rt. cervical 13 x 6 cm., lt. cervical 12 x 9.	21,750 4,500 3,300 cord 6000-8000	103 15 11	22	Stiffness of the left arm and leg. Constipated and impotent. Sensory level at T3. Died after 4 months.	Blood vessels thickened with fibrinoid material. Demyelination and necrotic foci. Neurones reduced in number and vacuolization.
2	Boden, 1948	73M	Carcinoma of pharynx and glottis	Four 5 cm. circle, 2 antero-lat., and 2 postero-lat.	2,000 cord 2,000	1	11	Paresthesias. Spastic quadriplegia. Slight sensory change. Double incontinence. C.S.F. normal. Died of myelitis after 1 month.	Intense necrosis between 2nd and 4th cervical segments.
3	Boden, 1948	56F	Carcinoma of pharynx posterior wall	Four 5 cm. circles, 2 antero-lat., and 2 postero-lat.	5,500 cord 5,200	17	10	Spastic legs, one spastic arm, bilateral sensory changes. Double incontinence. Died of of myelitis after 4 months	Large areas of necrotic degeneration and vessels conspicuously thickened.
4	Malamud et al., 1954	22M	Nasopharyngeal carcinoma	Lt. nasopharyn-cervical, rt. nasopharyn-cervical, and occipito-cervical	6,600 cord (?5,000)	20	10	Progressive weakness of one side. Pain and temperature loss in legs. Sensory levels at L1 on rt. and D7 on lt. Died after 4 mos.	Diffuse necrosis and demyelination. Petechial hemorrhages and "axonal reaction" of neurones.
5	Itabashi et al., 1957	72M	Lymphoepithelioma base of tongue and lt. neck	Direct lateral, contralat., antero-posterior, and postero-anterior	10,484 cord 10,484	27	15	Brown-Sequard-like syndrome progressed to flaccid quadriplegia. Died after 10 months.	Hemiatrophy of cord and diffuse degeneration of the remaining half. Degeneration of vessels.

TABLE 2

SUMMARY OF UNAUTOPSIED CASES PROBABLE POST-IRRADIATION CERVICAL MYELOPATHY

Case No.	Author	Age and Sex	Diagnosis	Field	Total r (air)	Duration of treatment (days)	"Free" interval (months)	Clinical findings	Follow up
1	Smithers et al., 1943	61M	Intraepithelial squamous cell carcinoma of esophagus		6,400 cord 5,800	39	15	Brown-Sequard syndrome with lesion at the level of 3rd and 4th thoracic segment. No block. C.S.F. Normal.	Survived treatment by 5 yrs. 10 mos. Died of cancer of prostate gland.
2	Boden, 1948	58M	Carcinoma pharynx posterior wall	three 10 x 5 cm., 1 anterior, and 2 postero-lateral	2,030 cord 2,225	1	4	Spastic quadriplegia. No incontinence.	Died of hemorrhage from primary after 6 months.
3	Boden, 1948	52F	Lymphosarcoma neck	Three 20 x 10 cm. triangular jig	3,500 cord 3,936	17	12	Brown-Sequard syndrome but commencing signs of affection of other side.	Alive after 46 months.
4	Boden, 1948	39M	Hodgkin's neck and mediastinum	Four 15 x 10 to neck and four 28 x 10 to mediastinum. 4 field jig	3,000 to each area cord 4,210	17	15	Spastic quadriplegia becoming flaccid. Bilateral sensory changes. Bladder and bowel incontinence.	Died after 4 months.
5	Boden, 1948	23F	Hodgkin's neck nodes	Three 20 x 10 cm. triangular jig	3,500 cord 4,320	17	11	Brown-Sequard syndrome.	Died after 11 months.
6	Boden, 1948	44F	Carcinoma pharynx post-cricoid	Small field Four 7 x 5 cm. 2 antero-lateral 2 postero-lateral	5,000 cord 5,060	17	5	Tingling in legs lasting 8 months.	Alive after 19 months. Symptom-free.
7	Boden, 1948	26M	Hodgkin's neck nodes	Large field Four 20 x 15 cm. 4 field jig	3,000 cord 3,000	17	3	Tingling in legs lasting 5 months.	Alive after 13 months. Symptom-free.
8	Boden, 1948	49M	Hodgkin's neck nodes	Large field Four 20 x 15 cm. 4 field jig	3,250 cord 3,250	17	6	Tingling in legs, radiating from neck, lasting 9 months.	Alive after 36 months. Symptom-free.
9	Boden, 1948	46F	Lymphosarcoma neck	Large field Two 20 x 15 cm. Two 20 x 10 cm. 4 field jig	3,250 cord 3,250	17	1	Tingling in legs, lasting 3 months.	Alive after 39 months. Symptom-free.
10	Boden, 1950	47M	Carcinoma larynx (extrinsic)	Three 5 cm. circles, 2 antero-lateral, and 1 posterior	5,500 cord 4,900	32	70	Spastic quadriplegia. Indefinite sensory changes in limbs and trunk. C.S.F. protein 75 mg.	Alive after 84 months.
11	Boden, 1950	48F	Carcinoma thyroid	Four 15 x 10 cm. Four field jig	3,500 cord 3,500	17	13	Brown-Sequard syndrome. Level at D1 segment. C.S.F. protein 50 mg.	Alive after 30 months.
12	Boden, 1950	54F	Nasopharyngeal anaplastic neoplasm	Four 20 x 10 cm. Four field jig	3,000 cord 3,000	17	12	Numbness of right hand and leg lasted 3 months but still present occasionally.	Alive after 32 months.
13	Itabashi et al., 1957	41F	Carcinoma of larynx	Rt. lateral cervical Lt. lateral cervical Anterior cervical Posterior cervical	8,000 cord 8,000	38	4½	Weakness of legs and sensory loss in legs. Spasticity.	Alive after 42 months.

Ahlbom's (1941) 4 cases not included because of lack of individual detail.
1 not cervical myelopathy but included because of similar clinical picture.

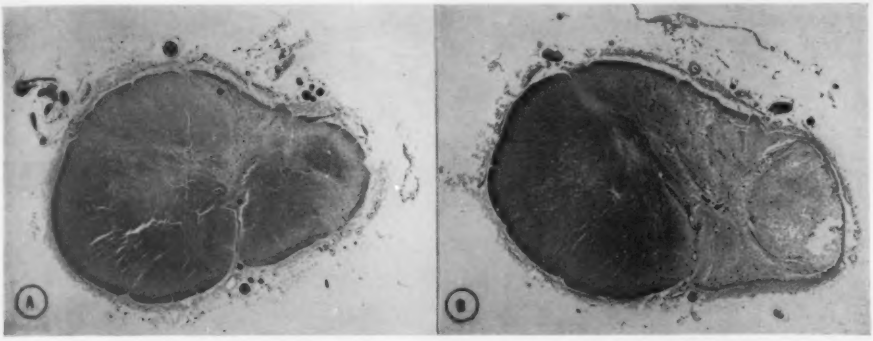

FIG. 1. *A.* Hematoxylin and eosin stain; C_2 segment of the spinal cord showing atrophy of the left hemisegment. *B.* Weil stain; C_2 segment of the spinal cord showing extensive damage to the left half of the cord with destruction of the posterior columns. Spongy state on the right.

because of pain. There was a sensory level on the right for pain, temperature, and tactile sensations at C_6. A band of hypalgesia and hypesthesia was present on the left from C_8 through T_8. The entire left arm was hyperesthetic. There was loss of vibratory sense up to the level of the clavicles. Position sense was markedly diminished bilaterally in both upper and lower extremities. There was stereoanesthesia bilaterally. All the extremities were atrophic, but more in the upper than the lower extremities. Few fasciculations were noted. All extremities were flaccid. Deep reflexes were hyperactive throughout, predominantly so on the left. The achilles reflexes were diminished. Bilateral Babinski signs were present, and a Hoffmann sign was noted on the left. Cystometrogram revealed a small capacity bladder. Because of the patient's inability to void spontaneously, a suprapubic cystotomy was performed. The patient received a transfusion of 1,000 cc. of whole blood over two days because of anemia. After the cystotomy his condition took a downhill course, with increasing lethargy, until his death on April 1, 1956 due to respiratory difficulties.

Pathologic Report

The brain was relatively large, with normal configuration. The leptomeninges were slightly thickened. There was moderate arteriosclerosis of the cerebral arteries, especially the basilar artery. Coronal sections of the cerebral hemispheres revealed only minimal dilatation of the ventricles. Sections through the midbrain, pons, medulla, and cerebellum appeared grossly normal. The spinal cord was removed with the attached thickened meninges. The left half of the upper and middle cervical cord was considerably smaller than the right. Sections revealed areas of necrosis and degeneration of both the white and gray substance, mainly posteriorly and on the left. There was no gross evidence of neoplasm.

Microscopic examination of the cerebrum, brainstem, and cerebellum showed only thickening of the meninges and passive congestion. There were moderate arteriosclerotic changes in the meningeal and cerebral vessels.

Significant pathologic alterations were found in

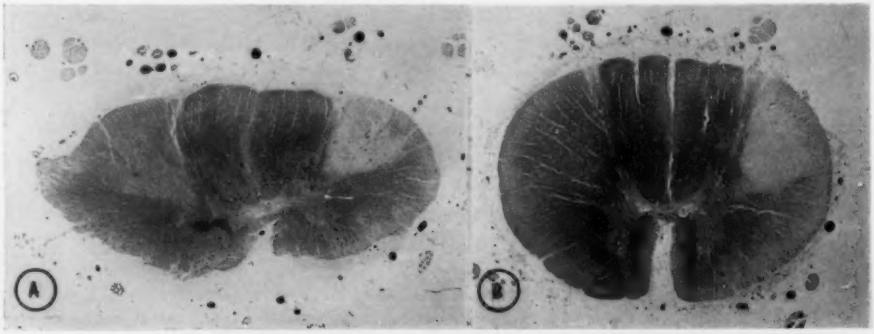

FIG. 2. *A* and *B*. Weil stain; lower cervical and upper thoracic segments, respectively, showing secondary degeneration of the left lateral corticospinal tract.

Ahlbom's (1941) 4 cases not included because of lack of individual detail.
Posterior cervical
9,000

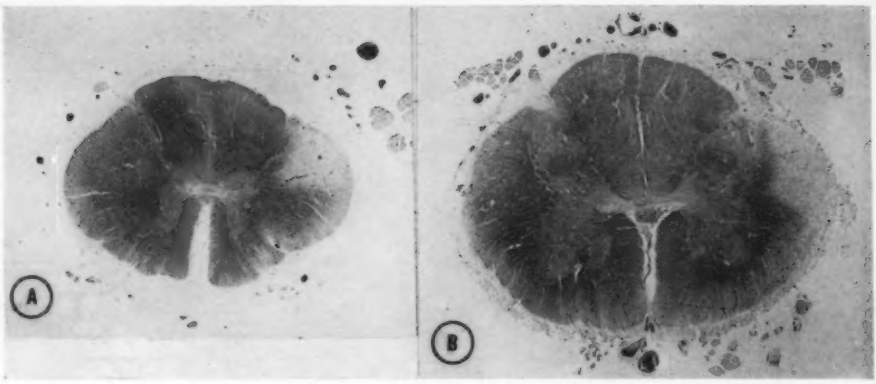

Fig. 3. *A* and *B*. Weil stain; midthoracic and upper lumbar segments showing degeneration of the left lateral corticospinal tract.

the spinal cord. Sections of the area of greatest damage as well as adjacent areas above and below were studied. The thoracolumbar segments were also studied for secondary effects. Low power magnification of hematoxylin and eosin and myelin preparations of the upper cervical (C_2 and C_3) cord showed almost complete destruction of the left hemisegment. This damage extended to include almost both posterior columns (figure 1). Below this, in the lower cervical and thoracicolumbar segments, there was marked demyelination of the left lateral corticospinal tract (figures 2 and 3). On high magnification, the greatest damage was seen in the C_3 segment. This was asymmetric, with the left half of the cord almost completely reduced to a mass of debris with gitter cells. There were many newly formed vessels which were markedly congested (figure 4). The posterior columns were also affected, but with diminishing damage to a point medial to the right lateral corticospinal tract. There was marked "spongy state" and proliferation of blood vessels in this area. The marginal zone of the cord showed considerable gliosis and formed a thin shell over the destroyed left half of the cord in which normal structures could not be identified. In the right anterior gray matter and posterior gray column, varying degrees of retrogressive changes of the neurons were seen. The leptomeninges appeared markedly thickened with extensive fibrosis. The blood vessels of the cord, venules and arterioles, showed marked acute passive congestion without evidence of thrombosis. Within the cord itself some of the arterioles showed considerable hypertrophy and degeneration of the tunica as well as hyaline changes (figure 5). There was no evidence of inflammation or neoplasm.

The segments above and below the main lesion

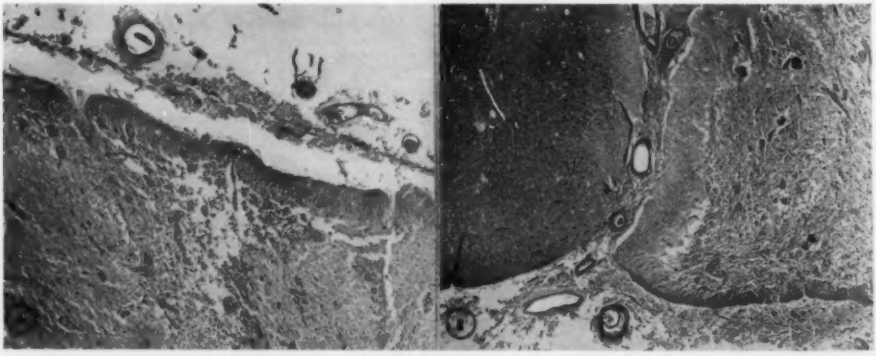

Fig. 4. *A*. Hematoxylin and eosin stain; high magnification of C_3 segment of the spinal cord showing extensive destruction, gitter cells, and thickened meninges. *B*. Hematoxylin and eosin stain; high magnification of the ventral portion of the cord showing complete destruction of both gray and white matter on the left, with gitter cells. The anterior veins and arteries are patent. Anterior horn cells remain on the right.

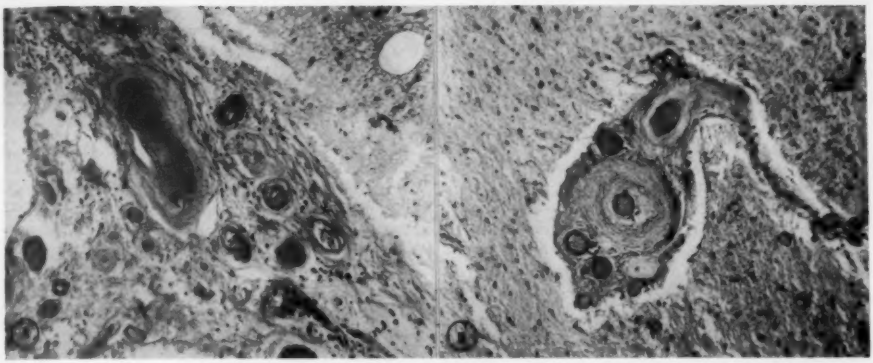

FIG. 5. *A.* Hematoxylin and eosin stain; acute passive congestion of vessels within the cord. *B.* Hematoxylin and eosin stain; photomicrograph of changes occurring in arterioles and veins within the spinal cord at the level of the most affected segment, showing hypertrophy and hyalinization.

showed similar changes in the left half of the cord, but to a much lesser extent. Sections stained with myelin technic showed complete destruction of the axis cylinders. The latter, when counterstained with red oil, showed considerable free lipoid material and gitter cells laden with fat (figure 6). Thoracic and lumbar segments of the cord showed congestion, the already indicated degeneration of the left lateral corticospinal tract (figure 3), and presence of numerous corpora amylacea in the marginal zone.

Case 2. A 41 year old white woman with a squamous cell carcinoma of the larynx received 8,000 air roentgens to the tumor over 38 days. Some 4½ months later she developed weakness and sensory deficit beginning in the feet and progressing to a spastic paraparesis. She was alive and ambulatory 39 months after the onset of her neurologic symptoms.

A 41 year old white typist first consulted her physician in September 1952 with a history of a foreign body sensation in the throat, change in voice, difficulty in swallowing food, and loss of 25 pounds of weight. She was found to have a finely granular tumor of the posterior pharynx. A biopsy was performed and the pathologic diagnosis was squamous cell carcinoma of the larynx. On September 9 an exploration of the cricoid area of the esophagus was carried out, but the tumor was inoperable due to extensive involvement. A tracheotomy was performed and extensive roentgen treatment was advised. From September 11 to October 18, 1952, 2,000 roentgens per port were administered to the right and left lateral cervical and anterior and posterior cervical ports, generated at 250 KV, 1 copper and 1 aluminum filter, at 50 cm. skin target distance. This was given at a rate of 250 roentgens per day (a total of 8,000 roentgens over a period of 38 days). The tracheotomy was discontinued on December 10, 1952. Follow-up examination revealed atypical mucoiditis and edema due to roentgen therapy and, except for a hoarse voice and inability to take solids, she seemed to be doing fairly well.

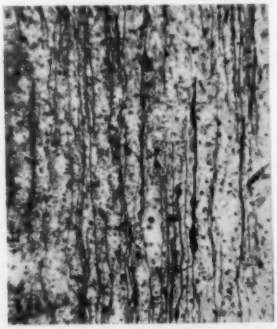

FIG. 6. Silver carbonate counterstained with red oil for fat; horizontal section of the spinal cord showing marked destruction and degeneration of axis cylinders and presence of free-fat.

In January 1953 the patient returned to work, but one month later she first noted general weakness. In March, when forced to stop suddenly, she felt a sudden electric shock-like pain in both legs. Later that month she noted ankle weakness, especially on the left. In April 1953 she stepped into a scalding bathtub of water with her left foot without feeling pain, and then noticed that she also had diminished pain sensation to the hip. In June 1953 weakness began in both ankles and progressed to involve the legs so that walking became an effort. Diminution of pain and temperature sensations was also noted in the right leg from the mid-calf down. There was no weakness of the arms, neck, and back. A myelogram was performed at this time and was reported to show no abnormality. Following this, there was little change in her condition until her admission to the University Hospital in February 1954, although

she did note a tingling sensation descending the posterior aspects of both legs from the hips down when she bent her head forward. There was no history of urinary incontinence or retention. She was constipated.

Examination in February 1954 showed the healed tracheotomy and incisional scars over the neck, and the skin of the neck showed pigmentation of irradiation. Examination of the larynx revealed slight edema of the arytenoids and the pyriform recess. Both vocal cords moved well and appeared normal, except for some vascularized scar tissue on the superior aspect of the right cord. No lymph nodes were palpable in the cervical, axillary, or femoral regions. On neurologic examination the cranial nerves were intact. Motor examination revealed diminished strength in the ankles, knees, and hips bilaterally, greater on the left. The lower extremities were spastic. There was loss of pain sensation with decreased temperature sensation to the groin on the left and to the knee on the right, with diminution of pain sensation to the umbilicus on the left and to the groin on the right. Light touch sensation was also decreased in these latter limits. Vibratory sensation was diminished in the left ankle, but position sense was reported as normal. Deep pain sense was absent in both ankles. The gait was unsteady and staggering, and the Romberg sign was positive. The deep reflexes were moderately hyperactive in the upper extremities and markedly so in the lower extremities, with bilateral Hoffmann and Babinski signs. There were unsustained patellar clonus bilaterally.

Spinal puncture showed a pressure of 90 mm. of water with no block. The fluid was clear and colorless, with 9 cells per cu. mm. The total protein was 22 mg. per 100 cc., the colloidal gold curve was 0000000000, and the mastic curve 000000. Roentgenograms of the chest and of the cervical, thoracic, and lumbar spine revealed no evidence of a destructive lesion and only minimal changes of hypertrophic spondylitis in the midthoracic region. Base view of the skull was normal. The outside myelograms were reviewed and were interpreted as normal. A diagnosis of cervical myelopathy was made, and the patient was discharged without therapy.

One week after her discharge she returned to her job as an office typist and remained at this job until October 1955, when she quit because of family responsibilities and not because of any physical disability. Beginning one month after discharge, a course of physiotherapy was given over a period of one year, along with vitamin B_{12} and iron injections once a week for the same period. There was some improvement in her gait, coordination, and strength. The shock-like sensation which she had when she bent her head forward disappeared, and she was able to move her head and back freely without symptoms. There was greater steadiness of gait and less staggering. Balance was occasionally poor. There was no change in the sensory level, but she claimed there was more sensation in the parts involved. There was some precipitancy of urination after her discharge, but this had cleared. Bowel movements were daily and regular without constipation or incontinence.

On re-examination in May 1956 it was noted that the gait was slow, cautious, unsteady, and limping, with circumduction of the right leg and simultaneous elevation of the right hip. She had more difficulty in propulsion when asked to walk barefooted than when she walked in medium-heel shoes. She was able to stand on the left foot alone, but not the right. The Romberg sign was negative. The cranial nerves were intact. The highest sensory level was to temperature sensation at the inguinal region on the left and just below the knee on the right. Vibratory sense was diminished at the left ankle but normal at the knee. Position sense and deep pain were intact. There was diminution of superficial pain a little below the temperature level. Light touch was also impaired in the same areas. There was sparing of the S_3 and S_2 dermatomes on the right. Sensation in the upper extremities was normal. Muscle mass and tone were normal in the upper extremities, but there was minimal weakness of the left wrist. Muscle mass was normal in the lower extremities, but there was moderate bilateral foot drop with shortening of the Achilles tendons, worse on the right. Other than a slight weakness of flexion of both hips, motor power of the lower extremities was fairly strong. There was minimal difficulty with coordinative movements of the lower extremities which could be attributed to spasticity and weakness. Deep reflexes were normal in the upper extremities and there were bilaterally symmetrical Hoffmann signs. The reflexes wre markedly hyperactive in the lower extremities, with a sustained clonus at the right ankle. Babinski and Chaddock signs were present bilaterally.

DISCUSSION

The clinical picture of postirradiation damage to the spinal cord is that of a progressive myelitis. The symptoms may begin with a numbness or tingling of the leg or legs, with spread to the opposite side, and also weakness which may be either spastic or flaccid. With cervical lesions the upper extremities may be involved. The syndrome is often progressive but not necessarily fatal. It may, however, terminate in quadriplegia and respiratory death, depending upon the sector and level of the spinal cord damaged by radiation. In many instances, there has been a Brown-Séquard syndrome with later progression to the opposite side. In our first case the neoplasm was in the left side of the tongue with extension into the left neck. Radiation was accordingly directed to the left, and the neurologic picture was first that of a left Brown-Séquard syndrome, which later progressed to flaccid quad-

riplegia terminating in death. In the second case the neoplasm was midline and the irradiation midline, and the clinical picture was essentially bilaterally symmetric, with spasticity in both lower extremities, although sensory changes were slightly greater on the left.

A "free interval" or latent period from one to 70 months between the conclusion of the therapy and onset of neurologic symptoms has been reported in the literature. This period in the two cases here reported was four and a half months and 15 months, respectively. Ten of 18 cases reviewed had their onset between ten and 15 months. The early symptom is that of pins and needles "often radiating down the spine to the limbs and brought on or aggravated by flexion or extension of the neck."[2] Our first patient complained of sharp pains in the neck with exertion, and the second had sudden electric shock-like pains down both legs and a tingling descending the posterior aspects of both legs with flexion of her head (Lhermitte's sign). Incontinence seems to be a poor prognostic sign, indicating a greater degree of damage. Five of Boden's 13 cases had fatal outcomes and, of the five, three had both bowel and bladder incontinence. In other fatal cases,[25,26] constipation and urinary incontinence were reported. Our first case had bowel and bladder incontinence terminally. The second patient, who survived, had only a transient urinary urgency.

Twelve spinal fluid examinations at various stages of the syndrome are reported in the literature. Except for a slight rise in the protein, the spinal fluid is essentially normal. The total protein ranged from 22 to 75 mg. per 100 cc. In our two patients the total proteins were 22 and 24 mg. per 100 cc. in fluid obtained at the onset of their neurologic symptoms. No block was present. Myelography performed in Malamud's case and the two reported by us were normal. Cervical spine roentgenograms were normal, except for hypertrophic arthritis, in all reported cases.

There is no positive means by which to appraise the immediate consequences of radiation therapy upon the central nervous system within the field. Factors such as field size, target distance, tissue dose, filtration, and duration of treatment obviously influence the development and course of the syndrome. While the outcome may be disastrous, the consequences are not invariably fatal or permanent. Indeed, Boden included among his first ten cases four patients who had only transient symptoms of tingling in the legs lasting three to nine months without objectively demonstrable neurologic signs.[2] They all eventually became symptom-free. If definite neurologic signs appear in addition to symptoms, the process seems irreversible. The ten cases which survived, as well as those not confirmed by autopsy, are listed in table 2. Of those with permanent neurologic deficits, including our two, eight were dead within 11 months after the onset, with an average of 5.5 months survival. The survivors were alive after 30 or more months after the appearance of neurologic symptoms.

Other than the brief report given by Ahlbom of his four cases, there have been only four cases reported in the literature with autopsy material. We have added one. In this case there was complete necrosis of the left half of the spinal cord, but the damage involved all of the remaining cord in varying degrees. New blood vessel formation was prominent, and the vessel walls showed marked hyaline changes. Some arterioles in the cord showed hypertrophy and degeneration of the tunica. Neurons of the gray columns showed retrogressive changes. Wallerian degeneration of the lateral corticospinal tract was seen in the thoracolumbar sections. The leptomeninges were thickened and fibrotic. Malamud and coworkers found diffuse necrosis and demyelination of white matter and similar thickening of intramedullary blood vessels, with deposition of a homogenous "fibrinoid" substance.[26] On the other hand, the gray matter was relatively spared although degenerative changes in neurons were reported. Stevenson and Eckhardt described extensive demyelination with small necrotic foci.[25] The leptomeninges were normal. They found extensive fibrous thickening of the smaller arteries and arterioles, with considerable narrowing of the lumina. Numerous fat-laden cells were present in the demyelinated areas. Neurons were reduced in number and showed degenerative changes. Wallerian degeneration of descending pathways was noted. Sparse pathologic findings were included in Boden's paper. Necrosis and thickening of the blood vessels and degenerative changes of the nerve cells were mentioned in the two autopsied cases. He cited Russell and co-workers[11] and expressed the view that the long latent period and the variation of the dose and field size with the severity of damage could reasonably be explained by the effect upon blood vessels. On the other hand, the direct effect of radiation in higher doses to the nerve cells cannot be ignored. In support of the theory

of vascular involvement with secondary effect, Boden cited a case with a sudden onset of a rapidly developing quadriplegia,[2] thought to be due to a thrombosis of a vessel of the spinal cord or hematomyelia. Warren[27] concluded that vascular interruption was the major factor in the radiation effect upon the brain and spinal cord, although direct radiation injury to nerve tissue could not be excluded. There may be swelling or necrosis of endothelial cells of blood vessel walls, and the same may occur with smooth muscles of the media.[28] Vascular changes may develop several weeks after irradiation, and occlusion of the lumen may result from endothelial thickening, proliferation and hyalinization of the connective tissue, and degeneration of the media.[28] McLaurin subjected the spinal cords of monkeys to intensive irradiation. The histopathologic changes were essentially those described by Warren above. However, he found that the alterations increased in severity with time, and suggested that the process was a dynamic one of progressive damage.[5]

SUMMARY

1. Two cases of postirradiation myelopathy are presented, one with pathologic findings. Sixteen other reported cases are reviewed, along with four undocumented cases.

2. The clinical syndrome is briefly discussed. The latent period after radiation therapy and before onset of neurologic symptoms is pointed out. In over half the cases this period was from ten to 15 months.

3. The damage to the nervous system appears to be primarily a secondary effect of vascular degeneration.

4. This syndrome probably occurs more frequently than the literature suggests, and the radiologist must be aware of the consequences of massive radiation therapy on the nervous system.

5. The possibility of post-irradiation myelopathy must always be borne in mind when symptoms of progressive spinal cord dysfunction develop in a patient who has received roentgen therapy for a lesion in the vicinity of the spinal cord.

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Glutamic-Oxalacetic Transaminase Activity in Spinal Fluid

Robert Katzman, M.D., Robert A. Fishman, M.D. and Eli S. Goldensohn, M.D.

GLUTAMIC-OXALACETIC TRANSAMINASE has been the subject of clinical interest since Karmen, Wroblewski, and LaDue[1] demonstrated that the serum level of this enzyme is markedly raised following acute myocardial infarction. Patients with acute parenchymal liver damage and with progressive muscle wasting also have high levels of transaminase activity in the serum.[2,3]

It has been shown experimentally that the rise in serum transaminase that occurs following heart or liver damage is due to release of the enzyme into the blood stream by degenerating cells.[4–6] Brain contains about as much transaminase as does liver.[7,8] However, in acute vascular accidents involving the brain, no consistent elevation of serum transaminase occurs.[7] Wakim and Fleisher[9] suggested that this may be due to the presence of a blood-brain barrier to transaminase and that the enzyme might be elevated in the spinal fluid following cerebral vascular accidents.

The present study has been made to determine glutamic-oxalacetic transaminase activity in the spinal fluid of patients with vascular accidents and other neurologic disorders.

METHOD

Enzymatic activity was determined by the spectrophotometric method of Karmen.[10] This method is an indirect one which measures the rate of oxidation of reduced DPN in a reaction mixture in which glutamic-oxalacetic transaminase is the limiting factor. Despite its indirect nature, this method gives results reproducible to within about 10 per cent.

In our determinations 0.2 ml. spinal fluid or serum was used. Spinal fluid and serum determinations from the control group were always made at the same time as those from the patients with neurologic disorders. Transaminase activity has been expressed as Karmen units at 25° C. This unit is a measure of the decrease of the optical density of the reduced DPN/minute/ml. Early determinations were run at room temperature; later they were made using a thermospacer accessory to maintain constant temperature. When necessary, appropriate temperature corrections were applied.[11]

RESULTS

Transaminase activity was estimated in the spinal fluid of 155 individuals. Forty-five constituted the control group. The remaining 110 cases included three with metastatic disease of the liver and three with psychiatric disorders. There were 104 patients with neurologic disorders, including 21 with intracranial mass lesions and 14 with acute nonhemorrhagic vascular accidents.

Simultaneous serum and spinal fluid transaminase determinations were made in 28 of the controls and in 73 of the experimental group. Five patients had serum transaminase activity above 45 units (table 1). All of these patients had evidence of heart or liver disease.

Controls

Spinal fluids were obtained from 45 patients undergoing spinal anesthesia for local orthopedic, gynecologic, or urologic procedures. The age of these patients ranged from 15 to 86 years. Spinal fluid transaminase activity in this control group ranged from 5 to 21 units, with a mean of 11.9 units (figure 1).

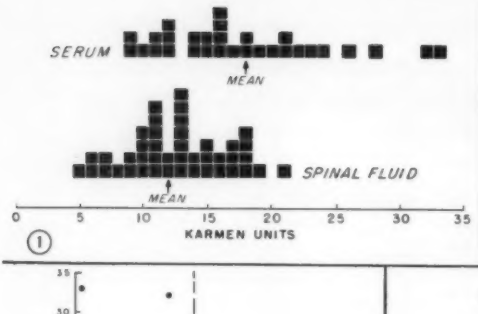
In 28 cases simultaneous serum and spinal fluid transaminase levels were determined. The serum activity ranged from 9 to 33 units, with a mean value of 17.8 units. The average lumbar spinal fluid transaminase was, then, about two-thirds that of the serum.

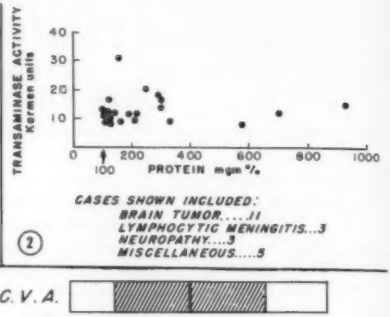
Activity in Ventricular Fluid—Total Spinal Fluid Protein

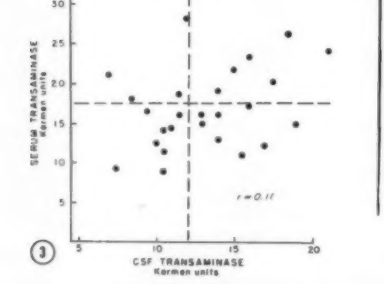
In five patients clear ventricular and lumbar fluids were obtained at the same time. Four of these patients had tumors and one had serous meningitis. The ventricular levels ranged from 3 to 17 units, with a mean value of 8.5 units, while the lumbar transaminase values ranged from 9 to 30 units, with a mean of 18 units. Hence, there appears to be a gradient of increasing transaminase activity between ventricle and lumbar sac similar to the protein gradient.

From the Neurological Institute, Columbia-Presbyterian Medical Center, and the New York Psychiatric Institute, New York City.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, April 26, 1957.







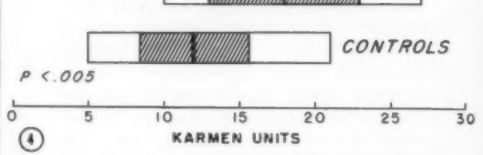


FIG. 1. Transaminase activity in control patients.
FIG. 2. Lack of relationship between cerebrospinal fluid protein and transaminase activity.
FIG. 3. Correlation of serum and cerebrospinal fluid transaminase activity in controls.
FIG. 4. Spinal fluid transaminase activity in cerebrovascular accidents.

However, in the 21 patients in whom the lumbar spinal fluid protein was elevated above 100 mg. per cent, there was no correlation between the spinal fluid protein and the spinal fluid transaminase activity (figure 2).

Blood-Spinal Fluid Barrier

The correlation between the spinal fluid and serum transaminase values in 28 controls is shown in figure 3. The correlation coefficient is 0.11, a value without statistical significance in this group. This suggests that the serum and spinal fluid values are independent of each other.

Other evidence for a blood-spinal fluid barrier to transaminase was supplied by Fleisher and Wakim,[12] who demonstrated that artificially infused transaminase concentrates in dogs did not readily cross from blood to cisternal fluid. Nydick and co-workers[13] reported one patient with rheumatic carditis and chorea who had a serum transaminase of 61 units and a spinal fluid transaminase of only 11 units.

Five patients with elevated serum transaminase associated with heart and liver disease are shown in table 1. In these patients the spinal fluid and serum values are apparently unrelated. Thus there does appear to be an effective blood-spinal fluid barrier to transaminase in man.

Elevated Spinal Fluid Transaminase

The transaminase activity was elevated in 12 patients (table 2). Four of these patients represent those with subarachnoid bleeding. Presumably, spinal fluid transaminase activity was elevated by the release of the enzyme by degenerating red cells.[14] Three patients had acute vascular accidents. The other five patients included two with progressive organic mental syndromes associated with cortical atrophy, one with pituitary adenoma, one with leukemia, and one with serous meningitis. The explanation for these latter elevations is not apparent.

Some conditions not associated with elevated spinal fluid transaminase are shown in table 3.

Cerebral Vascular Accidents

Spinal fluid transaminase activity was determined within the first ten days after the onset

TABLE 1
EVIDENCE FOR BLOOD-BRAIN BARRIER TO GLUTAMIC OXALOACETIC TRANSAMINASE

Disease	*Transaminase Activity* CSF	Serum
Liver metastases carcinoma	30	131
Liver metastases carcinoma	11	196
Liver metastases carcinoma	13	45
Myocardial infarction and cerebral thrombosis	13	125
Infectious mononucleosis	8	53

TABLE 2

CONDITIONS ASSOCIATED WITH ELEVATED SPINAL FLUID TRANSAMINASE ACTIVITY

	Elevated	*Normal*
Subarachnoid bleeding	4	0
Cerebral thrombosis and embolism	3	11
Cortical atrophy	2	2
Pituitary adenoma	1	2
Serous meningitis	1	2
Leukemia with cranial nerve palsy	1	0

of symptoms in 14 patients with acute vascular accidents. Patients with spinal fluids free of red cells were included in this series. The transaminase activity in the spinal fluid of these patients as a group was significantly elevated over that of the controls (figure 4). However, there is so much overlap between the groups that the difference between them does not appear to be useful clinically. Moreover, there is no correlation with clinical severity: only one of the five patients in whom the stroke was fatal had a spinal fluid transaminase value above the control range. Thus, we could not confirm the complete separation of those with strokes from the controls, as was reported elsewhere.[15]

Wakim and Fleisher[9] demonstrated a sevenfold rise in the transaminase activity of the cisternal fluid of dogs following the production of cerebral infarction by the intracarotid injection of red vinyl acetate. The difference between these results and those we have found in man may be related to a more severe and rapid tissue destruction produced by experimental infarction than occurs with the usual ischemic necrosis in man. Another factor might be the greater dilution of the enzyme in the more copious spinal fluid space of man.

TABLE 3

CONDITIONS NOT ASSOCIATED WITH INCREASED TRANSAMINASE ACTIVITY IN SPINAL FLUID

	Number of Cases	*Average (Karmen units)*
Intracerebral tumors	10	13
Multiple sclerosis	9	11.5
Convulsive disorders	7	10.5
Neuropathies	6	13
Lymphocytic meningitis	4	10.5
Psychiatric	3	12
Huntington's chorea	2	15
Cerebellar degeneration	2	11.5
Others	15	12.5

SUMMARY

1. In 45 controls glutamic-oxalacetic transaminase activity of the spinal fluid ranged from 5 to 21 units, with a mean of 11.9 units. Serum activity in the same patients ranged from 9 to 33 units, with a mean of 17.8 units.

2. Ventricular transaminase activity is less than lumbar fluid transaminase activity.

3. There is no correlation between spinal fluid transaminase values and spinal fluid protein level.

4. Spinal fluid transaminase values are independent of serum transaminase values.

5. Elevated spinal fluid transaminase values were found in 12 of 104 patients. Elevated values occurred in four out of four with subarachnoid bleeding and three out of 14 with acute nonhemorrhagic cerebral vascular accidents.

6. The average transaminase activity of the spinal fluid in the 14 patients with cerebral infarction was significantly higher than that of the control group. However, there was considerable overlap between these two groups.

We wish to express our appreciation to Mrs. Ruth Harris who carried out the transaminase determinations.

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Mental and Emotional Changes in Epileptic Patients on Continuous Anticonvulsant Medication

A Preliminary Report

Nathene Loveland, Ph.D., Bushnell Smith, M.D. and Francis M. Forster, M.D.*

CLINICIANS who deal with epileptic patients are continually faced with the question of possible mental and emotional side effects of new anticonvulsive drugs, and even for the older anticonvulsant drugs there is no adequate survey of changes in the patient's adjustment to his environment on continuous medication. The present research was designed to throw light on this problem, namely, "do anticonvulsive drugs affect the person's ability to cope with his environment quite aside from their efficacy in controlling seizures, and if so, what is the nature of the changes?"

GROUPS STUDIED

An epileptic group and an individually matched control group were studied. The epileptic group was drawn from the Georgetown University Medical Center Out-patient Epileptic Clinic and from the private practice of two of the authors. The patients had to meet the following three criteria to be accepted in the research group: 1) no progressive neurologic organic disease, 2) not mentally defective, and 3) no gross psychiatric problem.

Table 1 shows the composition of this group as to race, sex, age, education, and full scale IQ on the Wechsler Bellevue intelligence test. Table 2 shows the composition of the group as to age of onset of epilepsy, etiology, seizure type, focus of electroencephalographic abnormality, and seizure ratings based on the frequency and severity of seizures.

Seizure rating:

0—No seizure or interseizure difficulties.

1—Occasional (not more than two per week) lapses (flashes, dizzy spells, auras, or abortive seizures with a period of confusion of a few seconds' duration); mild petit mal seizures (five or less per day).

2—More than five petit mal seizures per day, the petit mal usually lasting longer than ten seconds, or one grand mal seizure per month, or up to three psychomotor attacks per month.

3—More than one grand mal seizure per month or more than three psychomotor seizures per month.

A carefully matched control population was obviously necessary, since we needed measures of practice effect and other changes due to the passage of time before we could determine whether any of the changes observed were due to the drugs. For humanitarian reasons, it is impossible to withhold medication from epileptic patients needing it. Therefore, controls were drawn from a non-epileptic population.

The adult control subjects were selected from army enlisted personnel. The children and adolescents were drawn from the public school system. For each epileptic patient a well matched control subject was found. Absolute matching was achieved for color, sex, and time interval between tests. Very close matching was attained for age, IQ, education, and socioeconomic status. Table 1 shows the composition of the control group as to age, sex, color, education and IQ, as well as the correlation between the matched groups.

DRUGS USED

No patient's medication was prescribed or varied for research purposes but was based solely on the neurologist's decision as to the individual's requirements. Thus, this is a statistical and not an experimental study. It was not possible to get any large group of patients on the same medication over the period of time studied. Therefore, this is not an adequate test of the effect of any particular drug, but a statistical study of the effects of varied anticonvulsant medication on our group as a whole.

Table 3 shows the medication these patients were taking for at least three months prior to the time when they came to us for seizure control and their medication during the three-month inter-test interval. Checks made with the patients and their interested relatives in-

From the neurology department, Georgetown University Medical Center, Washington, D.C.

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*Present address is Division of Neuropsychiatry, Walter Reed Army Institute of Research, Washington, D.C.

TABLE 1
COMPOSITION OF EPILEPTIC AND CONTROL GROUPS AS TO RACE, SEX, AGE, EDUCATION, AND IQ

	Epilepsy	*Control*	*Correlation*
Race			
Negro	5	5	1.00
White	21	21	
Sex			
Male	13	13	1.00
Female	13	13	
Age			
Mean	29.9	29.8	.99
Range	9 yrs. to 68 yrs.	10 yrs. to 63 yrs.	
s	15.5	14.9	
Education			
Mean	10.2 grade	10.5 grade	.89
Range	4th gr. to coll. grad.	4th gr. to coll. grad.	
s	3.1	2.7	
IQ			
Mean	101.2	102.9	.90
Range	77–126	86–129	
s	13.3	11.4	

dicated that the medication was taken regularly as prescribed.

PSYCHOLOGIC TESTS USED

A pilot study of eight months' duration was done in the search for valid, reliable, sensitive, and comprehensive measures of total adjustment. Special effort was made to include those aspects of the person's adjustment to his environment which clinicians who have worked with epileptics have felt might be affected by anticonvulsant drugs (for example, reaction time, accuracy, evenness of functioning, flexibility, judgment, memory, emotional stability, and motivation).

Reliability checks (blind scoring and later re-scoring) on all tests during the pilot study caused us to drop some of the tests tried and to modify others.*

The tests finally selected are listed in table 4, along with the qualities they were used to assess and the scores derived and analyzed therefrom.

The battery of tests required about an hour and a half to administer. The retests were usually administered in the same room as the original tests and were always administered in the same order to avoid test-induced differences in fatigue. Exactly the same test forms were used in both test No. 1 and test No. 2.

All tests were scored quantitatively except for the Rorschach test. In dealing with the Rorschach test, average changes in any particular score do not always mean the same thing, since the interpretation of changes depends not only on the base line from which the comparison is made but also on the interrelationships of all the separate scores. Thus, interpreting average changes in the light of mean base lines alone may be misleading. Therefore, in the case of each epileptic patient and his matched control, a blind comparison of the test-retest Rorschach records was made as to adequacy of total adjustment on the basis of the record as a whole. Though global analysis is the best way of using this test, it is much more subjective than scoring, making a reliability check especially desirable here. An experienced clinical psychologist independently scored and made blind over-all test-retest comparisons of the Rorschach records of every fifth epileptic and his matched control, and the results showed extremely high agreement with ours.

CLINICAL RATINGS

The neurologist rated each patient on adequacy of total adjustment at the time of retest, as compared with adjustment at original testing. Also, a psychiatric social worker experienced in working with epileptics interviewed most of the patients each time they were tested and made a similar independent

*The following is the list of tests tried out and dropped when the pilot study revealed them unsuitable for our purposes for various reasons: Draw a person test, Bender Gestalt test, Wechsler memory for designs test, Hall's body sway test of suggestibility, Cattell's tests of perseveration, Wells & Ruesch manual color naming test, filled and unfilled time estimates tests, Loveland's continuous processes test, Loveland's coding test, Loveland's insoluble maze test, writing figure 8 test, Petrie's anagram test for persistence at a task, Petrie's self-ascribed traits test, Petrie's attitude to illness test, Petrie's specified kinds of words test, Thaler's body rhythms test.

TABLE 2

COMPOSITION OF THE EPILEPTIC GROUP AS TO AGE OF ONSET, ETIOLOGY, SEIZURE TYPE, AND SEIZURE RATINGS

Age Onset	*Mean* 18.6 yrs. of age	*Range* 4 yrs. to 45 yrs.			
Etiology	*Idiopathic* 6	*Symptomatic* 20			
Type Sz	*GM only* 9	*Psych. only* 6	*Foc. only* 3	*PM only* 2	*GM&PS* 4 *Other* GM&Foc. GM Ps& 2 PM
Focus-EEG	*Diffuse* 10	*Left Temp.* 7	*Left Frontal* 3	*Rt. Temp.* 2	*Other* Rt. frontal 4 Rt. hemis. Mult. temp. Rt. occ-temp.
Sz Rating	0	No. 1	No. 2	No. 3	
From onset of epilepsy to test No. 1		9	15	2	
For the 3 mos. prior to test No. 1	2	13	9	2	
During the 3 mos. inter-test interval	12	9	4	1	
	1 step worse	*Same*	*1 step better*	*2 steps better*	*3 steps better*
Sz Rating Change from the 3 mos. prior to test No. 1 to the 3 mos. inter-test interval	1	13	7	4	1

TABLE 3

MEDICATION PRIOR TO TESTING AND DURING INTER-TEST INTERVAL

		Medication	*Medication*
Group	*N*	For at least 3 months prior to test No. 1	During 3 months interval between tests 1 and 2
A	2	None	phenobarital
B	3	None None None	phenobarbital and Dilantin Dilantin Mysoline
E	2	Dilantin	Dilantin
I	2	Dilantin, Mysoline and phenobarbital	Dilantin, Mysoline and phenobarbital
C	4	Dilantin and phenobarbital Dilantin and Mysoline Tridione Mysoline	Dilantin and phenobarbital Dilantin and Mysoline Tridione Mysoline
O	3	Dilantin and phenobarbital	Dilantin, phenobarbital and Mysoline
U	2	phenobarbital	Dilantin
D	8	Dilantin Dilantin Dilantin and phenobarbital Dilantin and phenobarbital Mysoline and phenobarbital phenobarbital Meheroin Tridione	Dilantin and phenobarbital Dilantin and Mebaral Dilantin, phenobarbital and Mebaral phenobarbital Mysoline phenobarbital, Mysoline and 16332 (Lilly) Meheroin and Mysoline Celontin
Total	26		

clinical rating of their total adjustment. Further, her interviews with the patients and their relatives provided a check on environmental or situational changes (for example, school, job, or family changes for better or worse, or seizures near time of testing), which might modify test behavior and therefore should be considered in interpreting test results.

To avoid possible unconscious bias, the clinical psychologist was not given information on medication, diagnosis, or clinical ratings of the neurologist and social worker until after the tests had been analyzed.

PROCEDURE

On the same day or within a few days of the time the patient had his neurologic examination and electroencephalogram, he was interviewed and rated by the psychiatric social worker and tested by the clinical psychologist. Immediately thereafter he was started on his prescribed medication. Three months later the whole process (except the electroencephalogram) was repeated. This allowed a full month if necessary for adjustment of proper dosage of the drug to obtain maximum seizure control with minimum physical side effects and left at least two months when the patients were on constant dosage of the same drug or combination of drugs.

ANALYSIS OF DATA

Two kinds of groupings of the data were analyzed. The first comparisons were made on the basis of medication, the second on the basis of the epileptic composition of the group.

The test-retest changes of each control subject on each score were subtracted from the changes found in the matching epileptic patient. The difference between the changes represents the change in the epileptic free from the effects of practice, passage of time, and so on; if there were any psychologic side effects due to medication, they would appear in this difference score. If there were no such effects due to medication or to any intrinsic or situational aspects of epilepsy, the mean of this difference would be zero. Therefore the general statistical procedure was to make a two-tail t-test of the hypothesis that the mean of the differences equaled zero.*

This was done for the following groups:

1. The epileptic group as a whole, as compared with the control group as a whole.

2. To throw light on the question of the extent to which the length of time on medication** or the fact of change in medication might affect our results, tests of significance were computed separately for each of the three following subdivisions of the group as a whole:

a) Those who had had no medication prior to test No. 1, thus were on continuous medication exactly three months when retested (table 3, groups A and B).

b) Those who were on the same continuous medication for at least six months, that is, their medication was no different during the three month inter-test interval than it was for at least three months prior to test No. 1 (table 3, groups E, I, and C).

c) Those whose medication was changed at test No. 1 but who were on some kind of continuous anticonvulsant medication for at least six months (table 3, groups O, U, and D).

3. To check on whether some specific drugs or groups of drugs might be most responsible for changes found to be significant for the group as a whole or whether two or more drugs might produce changes in opposite directions in any given task, thus hiding the effect of medication for the group as a whole, the totals were subdivided and analyzed:

a) By groups homogeneous as to medication both during the inter-test interval and for at least three months prior to test No. 1 (the single letter groups, table 3).

b) By groups homogeneous as to medication during the three month inter-test interval, disregarding the medication or lack of medication prior to initial testing (three patients on phenobarbital alone, five on Dilantin alone, three on Dilantin and phenobarbital, three on Mysoline alone, and five on Dilantin, Mysoline and phenobarbital combined).

4. To check on whether different types of epilepsy might produce changes in opposite directions on any given task, thus obscuring the effects of the medication, and to throw light on whether the type of epilepsy rather than the medication might be responsible for

*In the case of the Rorschach test, since these scores have non-normal distribution, the non-parametric sign test was also computed. In the case of the seizure ratings, the Pearson product-moment coefficient of correlation was computed in all cases where the rank order of the means of the difference scores was linear when plotted against the rank order of the seizure ratings.

**This report covers only the first half of this project, namely assessment of the changes in epileptic patients on continuous medication over at least a three-month time interval. Reassessment of the same patients (on the same and on changed medication, involving a few additional drugs) and their individually matched controls over a longer time interval is still in process and will be reported later.

significant differences found between the epileptics and the non-epileptics, the totals were subdivided and analyzed by groups homogeneous as to:

a) Etiology.
b) Type seizure.
c) Focus of electroencephalographic abnormality. Table 2 gives the composition of these subdivisions.

5. To throw light on the extent to which frequency and severity of seizures might be affecting our results, the totals were subdivided and analyzed by groups homogeneous as to seizure ratings, as follows:

a) Seizure rating for the duration of the epilepsy, from onset to initial testing.
b) Seizure rating for the three months prior to test No. 1.
c) Seizure rating during the three month inter-test interval.
d) Change in seizure rating, comparing that for the three months prior to test No. 1 with that during the three month inter-test interval.

Table 2 gives the composition of these subdivisions.

RESULTS

The overwhelming majority of the test scores analyzed showed no changes in the epileptic group as a whole, or in the subdivisions described above, significantly different from the changes found in their individually matched controls.

Altogether some 2,000 tests of significance were made; only 44 were significant at the

TABLE 4
PSYCHOLOGIC TESTS USED, THE SCORES ANALYZED, AND THE QUALITIES ASSESSED

Test	*Score*	*Function*
Wechsler-Bellevue*	Full Scale IQ	Intelligence, over-all assessment
	Verbal IQ	Verbal intelligence
Form II	Performance IQ	Performance intelligence
	Information subtest	General information
and WISC*	Comprehension subtest	Verbalized practical judgment
	Digit span	Memory, attention span, flexibility
	Arithmetic	Arithmetic reasoning, concentration
	Similarities	Abstract reasoning
	Vocabulary	Verbal facility
	Picture arrangement	Social comprehension
	Picture completion	Differentiation of essential from non-essential detail
	Block design	Analysis and synthesis of spatial relations
	Object Assembly	Synthesis of fragmented configuration
	Digit symbol	Association of familiar with unfamiliar symbols
	Scatter	Evenness of functioning among these varied types of tasks
	Reaction time (picture completion)	Speed in differentiating the essential from the unessential
	No. errors (digit-symbol)	Accuracy in a coding task
Rorschach	Global rating	Adequacy of total adjustment
	No. responses	Productivity
	W, W%, Dd. Dd%	Organizing ability, perceptual modus operandi
	F%	Spontaneity in combining logical reasoning with affective feeling
	F+%	Clarity of the perceptual ass'tive processes
	A%	Stereotypy
	H%	Interest in persons or in self
	M (Sum)	Richness of inner life, creativity
	C (Sum)	Affective extrasensitivity
	FC	Adaptive affectivity
	CF	Impulsivity
	C	Non-adaptive affectivity
	Shading responses	Cautiousness, sensitivity, method of dealing with anxiety
	FM	Unacculturated drives
	m	Inner tension and conflict
	Popular responses	Conventionality of ideas
	Anatomy responses	Bodily preoccupation, hostility
	Space responses	Oppositional tendencies
	Ratio of A&H : Hd&Ad	Perceptual flexibility, hypercritical compulsiveness, insecurity
	Rejections	Hostility, anxiety, blocking, repression
	t, T	Reaction time and mean response time
Porteus maze	Maze score	"Common sense" intelligence (non-verbal)
	Age-ratio score	"Comon sense" IQ, prudence, foresight
	Q-score	Emotional stability
	Total response time	Sustained speed

TABLE 4—(Continued)

Test	*Score*	*Function*
Level of aspiration	Initial estimate	Self-confidence, motivation, judgment
	Sum of estimates	Self-confidence, motivation, time sense, judgment
	Achievement	Motor speed, motivation
	Sum est.—sum ach.	Practical judgment
	Trial 2, est.—ach.	Practical judgment
	Est. 3—est. 4	Reaction to frustration
Wechsler memory for stories:		
Story read to subject	Immediate recall	Immediate memory for meaningful material heard
	Delayed recall	Delayed memory for meaningful material heard
Story read by subject	Immediate recall	Immediate memory for meaningful material read
	Delayed recall	Delayed memory for meaningful material read
	Reading time	Reading speed
	Reading errors	Reading accuracy
Serial subtractions of 7 from 100 (Wells & Ruesch manual)	% errors	Accuracy in subtracting
	Time per response	Speed in subtracting
Continuous additions (modified) (Wells & Ruesch manual)	Number right	Simple adding facility, speed
	Percent right	Accuracy in simple adding
	Number attempted	Motivation, speed
	Range of no. rt. per ½ minute	Evenness of functioning
Knox cube (modified)	Complexity of pattern reproduced	Memory, attention span (non-verbal)
	Complexity of pattern reversed	Memory, attention span flexibility (non-verbal)
	Combined score	Memory, attention span flexibility (non-verbal)
Glad emotional projection test (modified)	Number pleasant	Projected mood changes
	Reaction time	Speed in making quality judgments
No. words thought of in one minute	Number words	Verbal fluency
	Number repetitions	Redundancy
	Number errors	Ability to follow simple directions

*Weighted scores were used in all the Wechsler-Bellevue subtests. In addition, the unweighted scores were analyzed on the digit span subtest for digits forward and backward separately, as well as for the combined forward and backward score.

5 per cent level of confidence or better. Although we list (table 5) and discuss each significant difference found, there is some doubt whether any of these would remain significant with a larger sample.

1. For the group as a whole, the following five significant differences were found:

a) The epileptics, on the average, improved the clarity of their perceptual-associative processes, whereas the non-epileptics worsened in this respect (F+ per cent in the Rorschach test). No specific drug or drug group analyzed was especially responsible for this change, nor was any of the other factors analyzed.

b) The epileptics showed a healthier expression of their unacculturated drives, whereas the non-epileptics did slightly less well in this respect (animal movement on the Rorschach test). The symptomatic epileptics and those epileptics taking Dilantin alone or Dilantin and phenobarbital were especially responsible for this change.

c) The epileptics showed decreased adaptive affectivity on retest, whereas the non-epileptics showed no change in this respect (form-color responses on the Rorschach test). The symptomatic patients and those whose medication was changed were especially responsible for this change.

d) The epileptics showed a decrease in verbal fluency, whereas the non-epileptics showed improvement in this respect (number of words thought of in one minute). The patients whose medication was unchanged, that is, who were on the same medication for at least six months, the patients with grand mal seizures only, and those with diffuse electroencephalographic abnormality, were especially responsible for this change.

e) The epileptics lowered their initial estimates of their motor speed, whereas the non-epileptics increased theirs (level of aspiration test). The patients on the same medication unchanged for at least six months, those with both grand mal and psychomotor seizures, and those with diffuse electroencephalographic abnormality were especially responsible for this change. However, since the motor speed achieved by the epileptics was less than their estimates while that achieved by the non-epileptics was more than their estimates, the change for both groups probably reflects more realistic goal-setting rather than a significantly different change in self-confidence or motiva-

TABLE 5

SIGNIFICANT TEST-RETEST CHANGES

Group	N	Test	Score	Mean Change Epil.	Mean Change Non Epil.	t	Level of Confidence
Total	26	Rorschach	F + %	+ 2.46	− 3.34	+ 2.126	.05
Total	26	Rorschach	Animal movement	+ 1.00	− .31	+ 2.545	.05
Total	26	Rorschach	Form color rs.	− .50	0	− 2.208	.04
Total	18*	Words in 1 min.	No. words	− .73	+ 1.42	− 2.284	.05
Total	15*	Level of aspiration	Initial est.	− 1.65	+ 1.04	− 2.844	.02
Groups A + B	4*	Memory for stories	No. delayed memories of story read by patient	+ 2.25	+ 5.75	− 5.422	.05
Groups E+I+C	7*	Words in 1 min.	No. words	− .29	+ 4.87	− 3.421	.05
Groups E+I+C	7*	Level of aspiration	Initial est.	− 4.29	+ 1.87	− 3.501	.05
Groups O+U+D	13	Rorschach	Form color rs.	− .62	+ .15	− 2.730	.05
Groups O+U+D	13	Rorschach	Anatomy rs.	− .31	+ 1.15	− 3.630	.01
Group I	2	Rorschach	Form %	−20.50	0	−41.000	.02
Group C	4	Rorschach	Form %	+ 9.25	− 4.00	+ 3.513	.05
Group B	3	Wechsler-Bellevue	Scatter	0	+ 1.67	− 4.991	.04
Group D	5*	Knox cube	Forward and back score	+ .40	− .60	+ 3.163	.05
Pb	3	Wechsler-Bellevue	Picture arr. wt'd score	+ 1.67	+ 5.33	− 5.500	.05
Dil & Pb	3	Wechsler-Bellevue	Block design wt'd score	− 1.33	+ 2.00	−10.000	.01
Dil & Pb	3	Rorschach	No. responses	+ 7.00	−11.67	+ 6.424	.03
Dil & Pb	3	Rorschach	Animal movement	+ .67	− 1.00	+ 5.000	.05
Dilantin	5	Rorschach	Animal movement	+ .80	− 1.00	+ 3.087	.05
Dilantin	3*	Porteus maze	Time score	−47.33″	+58.33″	− 4.479	.05
Dilantin, Mysoline and phenobarbital	3*	Continuous add.	Range of # correct per ½ min.	− 4.67	+ 3.67	− 6.932	.03
GM Szs	9	Wechsler-Bellevue	Reaction time on picture completion	−34.33″	− 1.56″	− 3.995	.01
GM Szs	5*	Memory for stories	No. immed. mems. of story read by patient	+ 3.40	+ 4.20	− 4.002	.02
GM Szs	5*	Memory for stories	No. delayed mem. of story read by patient	+ 1.60	+ 4.40	− 6.261	.01
GM Szs	4*	Porteus maze	Time score	− 2.50	− 7.75	+ 3.342	.05
Psych. Szs.	6	Wechsler-Bellevue	No. errors in digit symbol	− .17	+ 1.00	− 3.162	.05
GM & Psych Szs	2*	Level of aspir	Initial est.	− 4.00	+11.00	−15.000	.05
	2*	Level of aspir.	Sum of ests.	−11.50	+16.00	−55.000	.02
Focal Szs.	3	Rorschach	No. responses	+14.00	+ .50	+ 9.404	.02
	3	Rorschach	Form %	−23.50	+ .50	− 5.547	.05
Diffuse EEG Abn.	8*	Level of aspir.	Initial est.	− 3.50	+ 1.62	− 2.821	.05
EEG Abn.	9*	Memory for stories	No. immed. mems. of story read by patient	+ 2.22	+ 4.00	− 2.342	.05
EEG Abn.	9*	Memory for stories	No. delayed memories of story read by patient	+ 1.00	+ 3.55	− 2.611	.05
Left Temp. Focus	4*	Level of Aspiration	Goodness of judgment in adopting est. to achievement	+ .25	− 1.50	+ 3.653	.01
	7	Rorschach	Form color resps.	− .85	+ .14	− 3.240	.02
Idiopathic	6	Rorschach	Form %	−11.17	− .17	− 3.159	.05
Symptomatic	20	Rorschach	Form color resps.	− .55	+ .40	− 2.942	.01
Symptomatic	20	Rorschach	Animal movement	+ 1.20	− .40	+ 2.507	.03

Group	N	Test	Score	Seizure Rating 0	1	2	3	r
Seiz. Rating, Duration	26	Rorschach	Popular resps.		+1.800	− .459	−2.000	.519
Seiz. Rating Duration	26	Rorschach	Inanimate movement (m)		+1.222	− .333	−1.000	.409
Seiz. Rating Inter-test Interval	26	Rorschach	Animal movement (FM)	+2.417	+1.333	− 1.000	−2.000	.500
Seizure Rating 3 mos. prior to Test #1	26	Wechsler-Bellevue	Information	+3.000	+ .153	− .556	−1.000	.510

*Starred tests were introduced late in the pilot study, so that some of the patients missed taking them at initial testing.

tion between the two groups.

2. As for the subdivisions based on medication, considering medication both during and prior to inter-test interval, the following additional significant changes were found:

a) Only one of the 72 test scores analyzed yielded significant differences in opposite directions for different subgroups. Namely, among the patients who had been on the same medication unchanged for at least six months, those on Dilantin, Mysoline, and phenobarbital combined (group I, table 3) showed sig-

nificantly healthier spontaneity in combining logical reasoning with affect (form per cent on the Rorschach test), those on Dilantin alone (group E) showed no change significantly different from their matched controls, whereas the rest of the group on miscellaneous drugs (group C) changed in a less healthy direction in this respect. Both the idiopathic epileptics and those with focal seizures only also showed significantly healthier spontaneity scores than did their controls.

b) The patients who had been on no medication prior to initial testing (groups A and B) improved less in their delayed recall of the story they read themselves than did their matched controls. This was true also for the patients with grand mal seizures only and for those with diffuse electroencephalographic abnormality (see discussion for interpretation in view of overlapping of cases).

c) The patients whose medication was changed (groups O, U, and D) showed less hostility and/or bodily preoccupation, whereas their matched controls showed more (anatomy responses on the Rorschach test).

d) The patients who had no medication prior to initial testing and were taking phenobarbital during the inter-test interval (group B) showed no change in evenness of intellectual functioning, whereas their matched controls became more uneven in this respect (Wechsler-Bellevue scatter).

e) Group D of the patients whose medication was changed (no two exactly alike in the way they were changed) improved in their non-verbal memory, attention span, and/or flexibility, whereas their controls worsened in this respect (Knox forward and backward score).

3. As for the subdivisions based on medication during inter-test interval, disregarding medication or lack of it prior to initial testing, the following additional changes were found significant:

a) Patients on phenobarbital alone improved less than did matched controls in their social comprehension, as measured by the Wechsler-Bellevue picture arrangement subtest.

b) The patients on Dilantin alone speeded up, whereas their matched controls slowed down on the Porteus maze test.

c) The patients on Dilantin and phenobarbital combined did less well in their analysis and synthesis of spatial relations, whereas their matched controls improved in this respect (Wechsler-Bellevue block design test).

d) The patients on Dilantin, Mysoline, and phenobarbital combined functioned more evenly, whereas their matched controls showed increased unevenness of functioning on the test requiring sustained addition (range score).

4. As for the subdivisions based on types of epilepsy, the following additional changes were found significant:

a) The patients with grand mal seizures alone improved less in emotional stability (Q-score, Porteus maze test) and in their immediate memory of the story they read themselves than did their controls, but improved more than their controls in differentiating essential from nonessential details (Wechsler-Bellevue picture completion subtest).

b) The patients with psychomotor seizures only improved their accuracy in coding, whereas their controls became less accurate in this respect (Wechsler-Bellevue, errors in the digit symbol subtest).

c) The patients with diffuse electroencephalographic abnormality improved less than did their matched controls in their immediate memory of the story they read themselves.

d) The patients with left temporal foci improved in practical judgment, whereas their controls worsened in this respect (level of aspiration test, difference between estimate and achievement, trial No. 2).

5. As for the subdivisions based on frequency and severity of seizures, so few (only four of the 280 analyses made) of our tasks proved linearly and significantly related to the seizure ratings that we re-examined all our data, not just those scores that were linearly related, to look for qualitative trends that might not show up as statistically significant for any particular task but which might prove qualitatively significant if a substantial majority of the trends piled up in a single direction. However, we found about as many instances where the patients with the worst seizure ratings ranked highest in their test score improvement and those with few or no seizures ranked lowest as the other way around. The four instances found to be significant were:

a) The more favorable the seizure rating during the period of time from onset of epilepsy to test No. 1, the more favorable the change in conventionality of the patients' perceptual-associative processes (popular responses on the Rorschach test).

b) The more favorable the seizure rating from onset to initial testing, the less favorable the change in inner tension and conflict revealed (inanimate movement on the Rorschach test).

c) The more favorable the seizure rating during the inter-test interval, the more favorable the change in expression of unacculturated drives (animal movement responses on the Rorschach test).

d) The more favorable the seizure rating during the three months prior to initial testing, the more favorable the change in the patient's general fund of information (Wechsler-Bellevue information subtest).

It will be noted that the significant changes found were as often as not in the direction of a healthier adjustment.

6. As for the results from the "adequacy of adjustment" ratings of the Rorschach records as a whole, it proved impossible to rate these records with confidence as better or worse in total adjustment. This seemed due both to the fact that there was relatively little change from test to retest in most cases and because in almost no case was the change simply or consistently in one direction. However, when a choice was forced, about as many of the tests as retests were selected as better adjusted, and this was equally true for the epileptics and the non-epileptics. Further, those patients who were selected as better adjusted were scattered randomly among our medication and epilepsy type subdivisions. Nor were there any systematic differences between the comparative ratings of the epileptics and their matched controls.

Thus, these results are consistent with those drawn from the analyses of the test score changes in that no systematic changes in the total adjustment of these patients was found.

7. As for the clinical ratings, the neurologist rated 20 of the 28 epileptic patients as unchanged and four as having less adequate adjustment on the second rating as compared with the first. The other two could not be rated because of inadequate records. No homogeneity of medication or epilepsy type or severity existed in the four cases rated as poorer.

The psychiatric social worker saw 18 of the patients both times. She rated nine as unchanged, five better, and four showing poorer total adjustment at retest times. Again, analysis of each rating group revealed no homogeneity of medication, epilepsy type, or severity. Only one of those rated "poorer" by the psychiatric social worker was also rated poorer by the neurologist, and on the psychologic tests this patient showed more improved than lowered test scores.

Obviously, neither of these judges rated the group as a whole as changed very much in total adjustment from test to retest.

DISCUSSION

It should be noted that we are investigating test-retest changes and that we offer no evidence at this time as to whether the epileptics at first testing were significantly different from their individually matched controls. We are not investigating the question of whether there is such a thing as an "epileptic personality" or other intrinsic differences between epileptics and non-epileptics, but rather whether continuous medication changes, whatever the original adjustment was, significantly differently from the changes one would expect from "normal" practice effect and ordinary changes due to the passage of time.*

Our most important finding is our negative results—namely, that when epileptic patients on continuous medication are carefully matched with non-epileptics, so few significant differences (44 out of 2,000) are found between them in test-retest changes.

In the cases where we did find significant differences in test-retest changes between the two groups, the fact that our controls are non-epileptics raises the question whether the differences were due to the medication or to possible intrinsic differences between epileptics and non-epileptics. Thus, we cannot causally relate the relatively few differences to medication but can only report them and allow their interpretation to await further study.

Our analysis of data by types and severity of epilepsy seemed necessary, since our epileptic group was far from homogeneous in these respects and too small for subdivision into groups homogeneous both in these respects and in medication. However, here, too, our most important finding is the paucity of significant differences found. As described above for medication, the same objections maintain here in trying to relate the significant changes found to type or severity of epilepsy, since our controls are non-epileptic.

In the cases of test scores where significant differences were found both for subgroups homogeneous as to medication and for subgroups homogeneous as to one or more aspects of the type or severity of the epilepsy, the fact that there was usually some degree of overlapping of cases only adds to our reasons for be-

*The few environmental or situational changes reported by the social worker which occurred during the period of time studied were found to have no systematic effect on the test results.

ing unable to interpret causally the significant differences found.

A continual problem with a statistical analysis such as ours is that when so many t-tests of significance and correlation coefficients are computed on regroupings of the same data, some spurious "significant" differences can be expected to appear by chance. This is especially important to keep in mind in this study where we dealt with subgroups of such small numbers. Thus, any, perhaps most, of the relatively few "significant" differences found may be spurious.

However, even if all these "significant" differences found should prove with larger samples to be really significant and causally related to the medication, they would not contraindicate continued prescription of these drugs, since the changes are as often as not in the direction of a healthier adjustment.

Attention is called to the fact that our sample represents a highly selected group of epileptics. When we ruled out epileptics with other conditions (gross mental, psychiatric, or changing neurologic abnormalities) that might be expected to obscure assessment of the effects of medication, only 34 patients could be found in a lively out-patient epileptic clinic and in the private practices of two neurologists over a 27-month period (eight of these 34 dropped out because of moving from the area or similar reasons). Thus, this group is one in which epilepsy is almost the sole symptom and for the most part they carried on relatively normal lives. Our conclusions cannot be applied blindly to epileptics with gross organic or functional difficulties.

SUMMARY AND CONCLUSIONS

Out of some 2,000 two-tail t-tests of significance and Pearsonian product-moment coefficients of correlation computed on the test-retest changes in 72 different test scores, only 44 were found to be significantly different for the epileptic group as compared with their non-epileptic individually matched controls.

From the evidence available in this study, we cannot adequately interpret the meaning of the changes that *were* found to be significant, nor relate them causally to medication, nor even be sure that the significance is not spurious.

However, our test data, supported by the clinical ratings, yield negative evidence of interest to the clinician who prescribes anticonvulsant drugs, namely, that the drugs administered to this group of epileptics had little if any effect on their total adjustment to their environment as measured by these tests and ratings, and, to the extent that the medication might have had an influence, it was as often favorable as unfavorable.

We are indebted to the division of neuropsychiatry, Walter Reed Army Institute of Research, for making available to us the adult control subjects, sufficiently matched to our population from Army records and tests so that only about four subjects had to be tested by us for every one used as a control. Similarly, Mr. Gregory, principal of Western Junior High School, and Miss F. Parker, principal of Potomac Elementary School, both of the Montgomery County, Maryland, public school system, partially screened and made available to us the child and adolescent controls.

The authors also express appreciation to the following persons who contributed to the study: Dr. Margaret Thaler Singer, Division of Neuropsychiatry, Walter Reed Army Institute of Research; Mrs. Dorothy Smith, Georgetown University Medical Center; Dr. Ardie Lubin, Division of Neuropsychiatry, Walter Reed Army Institute of Research.

DIAGNOSTIC NOTE

Some Notes on the Gerstmann Syndrome

Josef Gerstmann, M.D

In spite of an extensive bibliography on the syndrome of finger agnosia, disorientation for right and left, agraphia, and acalculia, and of the virtually universal recognition of it as a well-defined neurologic symptom-complex resulting from localized involvement of the parieto-occipital region of the dominant hemisphere, there are still misconceptions about the syndrome, as evidenced by an article recently published in this journal.[1] Consequently, I would like to present once more the clinical-phenomenologic definition of the syndrome and its associated features and to review the subject briefly in the light of present day experience.

In a series of papers[2] and lectures during the course of many years, I have stated that finger agnosia, first described and so designated by me in 1924,[2] is a disorder of the body image proper. It consists in a *primary* disturbance or loss of ability to recognize, identify, differentiate, name, select, indicate, and orient as to the individual fingers of either hand, the patient's own, as well as those of other persons. Subsequent to this gnostic disorientation with respect to the fingers, restriction in their separate kinetic realization occurs not infrequently. It is characteristically associated with lack of recognition and orientation for the right and left sides in respect to the patient's own body, as well as that of other persons, often with special reference to the hands and fingers. These disorders are commonly combined with an isolated disability for writing—dys- or agraphia—and an isolated disability for calculation—dys- or acalculia—of differing severity and definite character, both types of disorder varying in significant respects from the aphasic, apraxic, and spatial-agnostic types. The disturbances tend to appear in varying degrees of development. All these symptoms group themselves phenomenologically and psychologically into a well circumscribed syndrome. Investigations in a large number of cases of this type have so far failed to reveal any evidence of psychic or intellectual disorder, aphasia, apraxia, or other manifestations of agnosia (particularly with regard to outer space and objects therein) or of motor or sensory changes to which the symptom-complex of finger agnosia and its accompanying individual features could be related. The syndrome has, therefore, been considered primary. There is extensive evidence (in accordance with my original assumption) that the syndrome of finger agnosia, with disorientation for corporeal right and left, agraphia, and acalculia, is usually caused by a pathologic process affecting the lower part of the dominant parietal or parieto-occipital region of the brain, namely, in that nodal area which corresponds to the angular gyrus in its transition to the second occipital convolution; it seems to be the only complex, though isolated, involvement of the body scheme proper which can be found as a result of, or developing from, a focal cerebral lesion.

Many examples of findings at autopsy or biopsy that have established and corroborated the above-mentioned localization of the lesion could be cited, both from personal experience and from extensive literature on the subject. I shall refrain from doing so, except for a most interesting case reported by Delay.[3]

A 42 year old woman suffered from epileptic crises following electroshock therapy. The attacks were first attributed to the treatment, but later investigations showed that the seizures as well as the mental condition, namely the depressive state, for which she received shock treatment were actually caused by a cerebral tumor. A careful neurologic examination showed, apart from "very active tendon reflexes and an irregular Babinski on the right side," the existence of the syndrome of finger agnosia, right-left disorientation, agraphia (not accompanied by disturbance in spoken and internal language), and acalculia. In conformity with previous findings, this characteristic complex of symptoms suggested a lesion of the transitional region between the lower parietal and the middle occipital convolution on the left side. A ventriculogram showed moderate dilatation of the right ventricle with reduction of the left occipital horn and massive compression of the ventricular system on the left, all indicating the diagnosis of a left parieto-occipital tumor. Operation was performed and the tumor removed. The patient recovered completely.

The phenomenon of finger agnosia is quite characteristic in genuine cases. A patient with this disorder cannot orient himself with regard to the individual fingers of either hand (his own, as well as those held out by the examiner). He cannot recognize them in any way

240 Central Park South, New York City.

corresponding to the normal; he cannot differentiate his fingers (thumb, index, middle, ring, and little finger) at all, or not fully; he cannot name them correctly, cannot indicate specific fingers on command, and cannot imitate given finger postures of the examiner, and he commits striking errors in appropriate tests. This occurs, it should be noted, in spite of the patient's often remarkably good general mental condition, in spite of his adequate theoretic knowledge of the hands and fingers, in spite of preserved, or at least sufficient, verbal comprehension and expression, in spite of sufficient vision to guide him, in spite of appropriate recognition of objects and their spatial relations outside the body and proper orientation in external space, and in spite of the absence of any interfering sensory or motor disorders. The same is true of the accompanying disorientation for right-left in the sphere of the body (somato-lateral agnosia). The latter likewise occurs in spite of the patient's familiarity with the connotation of the terms "left" and "right," and in spite of his ability (in typical cases) to distinguish sidedness in outer space, namely in respect to inanimate objects outside the body. As a rule, the patient does not become aware of his errors spontaneously and is quite helpless in controlling them.

Finger agnosia may thus be defined as a *primary* conceptual-symbolic disturbance or loss of the capacity for recognition and orientation in one area of the body. As far as all the other parts of the body (including the feet and the toes) are concerned, ability to recognize them and to orient with reference to them remain essentially unaltered. It is as though, in finger agnosia, the body image or body scheme were affected in one sphere only, and indeed functionally in the most significant, differentiated, and vulnerable one—the sphere concerned with the individual fingers—as though the optic-tactile-kinesthetic image pertaining to the fingers were split off from the total body image, the finger scheme from the total body scheme.

The phenomenologic association of finger agnosia and disorientation for right and left on the one hand, with a disturbance or loss of ability to write (dys- or agraphia) and a disturbance or loss of ability to perform calculations (dys- or acalculia) on the other, into a well-defined syndrome is quite significant. This combination is fairly understandable if one remembers how important the individual fingers and their right-left laterality are in acquisition of the functions of writing and calculating.

The function of writing is inconceivable without the highly integrated level of morphologic and physiologic differentiation of fingers and their conceptual representation that has developed in man, and continuation of intact ability to write is incompatible with disintegration of this development. The association of finger agnosia with disorders of writing could be interpreted also as due to the necessity of awareness of one's fingers while writing. One could assume that correct writing depends on the integrity of the body image and, in particular, of the part of it corresponding to the fingers.

The association of disorders of calculation with finger agnosia raises a problem of great interest from an anthropologic rather than clinical-psychological standpoint. Fingers and hands seem to play an essential role in the evolution of the whole system of numeration. It is commonly known that fingers supply the first aid in learning to calculate. The first arithmetic operations of children are performed on the fingers of each hand. In the counting of primitive peoples, both in remote times and also today, fingers and hands play an important, if not integral, role. Counting upon fingers was probably a universal practice in ancient times; it is significantly reflected in the Latin word "digitum" to stand for both "finger" and "number" among the Romans. It still stands for both in the English word "digit." Schilder[4] and particularly Critchley[5] gave numerous illustrative and relevant examples properly bearing upon the matter in question. It appears legitimate to say that between consciousness of fingers or finger gnosis and calculation there has existed an intimate functional interdependence and interaction from the earliest period in man's development.

The natural question which now arises, after discussion of the relationship between the various features of the syndrome, is whether any common principle lies behind its four cardinal manifestations, that is, finger agnosia, right-left disorientation, agraphia, and acalculia. Space will not permit an appropriate elaboration of this question. Various investigations seem to indicate that it is justified to look upon the impairment of the functions involved in the four typical phenomena of the syndrome as an expression of a fundamental disorder of a genetically, structurally (in a wider sense), physiologically, and psychologically integrated entity, namely, the body image.

Benton and Meyers[1] cite a case reported by Badal[6] (a French ophthalmologist) concern-

ing a young female patient who, following severe eclampsia and after a transitory confusional state and temporary blepharoptosis, developed—apart from a bilateral inferior hemianopsia and a significant constriction of both visual fields—a complicated neurologic symptomatology, which, in my judgment, merely constitutes an interesting example of the well known condition of visual disorientation or visual-spatial agnosia. Badal described the condition at great length, though often employing qualitatively inadequate technics of examination and leaving many important questions unanswered. Benton and Meyers[1] expressed in their article the opinion that the Badal case "might be interpreted as a 'Gerstmann syndrome,' unrecognized as such." This opinion is wholly unfounded. As can readily be seen from a careful study of the rather extensive report of Badal, his case is in no way a description or representation of what has become clinicopathologically established as the Gerstmann syndrome. The latter is primarily related to disorientation in personal space, the former to that in extrapersonal space.*

Benton and Meyers stated in their article that the Badal case report "was evidently not unknown to neurologists 50 years ago" and was "quoted rather extensively from" by Pick in 1898. This was because the clinical condition of visual disorientation was a subject of much investigation in the 1890's. Benton and Meyers wonder that this early report "appears to have been overlooked in recent years," not having been mentioned in such current monographs of topical importance as those of de Ajuriaguerra and Hecaen, Critchley, Hecaen and de Ajuriaguerra, and Nielsen which appeared in the years between 1946 and 1953, and, I may add, in others which had preceded them (Poetzl, Quensel, and so on). The logical explanation for omitting the Badal case from the various bibliographies and treatises in the twenties and thirties or even earlier could only be that the knowledge of the clinical condition of visual disorientation or visuospatial agnosia had become well established, and the interest in the Badal case report (published in 1887) had long faded into oblivion as a scientific contribution to the subject.

The clinical picture of the Badal case consisted principally of a profound disorder of visual-spatial and more subtle visuopsychic functions resulting in severe defects of orientation in outer, that is, extrapersonal, space and of recognition and appreciation of objects in their spatial relationship to each other, their position, location, distance, and size, with gross errors in their absolute and relative localization in the environment. The patient also showed impairment of visual attention, inability to fixate, loss of topographic memory with impairment of spatial-directional orientation, marked visuo-spatial and spatial-agnostic as well as constructional defects concerning the abilities of writing (particularly copying), reading, (and to a lesser degree) calculation, inability of simple drawing (from memory or model) and disorder of various other spatial manipulations, spatial confusion of right and left sides, disturbance of tactile localization and two-point discrimination, and loss of ability to localize fingers subjected to tactile or algesic stimuli, indicating that these disturbances were primarily perceptual-spatial (atopognostic) rather than somatognostic in origin. There were also other disturbances such as various apractic defects, particularly dressing apraxia, some auditory-spatial disorientation, and some degree of temporal disorientation. All these disorders were regarded by Badal as a result of and related to profound defects of what he called "the sense of space."

Badal did not reach a diagnostic conclusion in his case. He merely posed the question as to whether the condition shown by his patient was "purely functional" (in terms of traumatic hysteria) or "due to organic lesion," but without arriving at a definite decision. There can, however, be no question of its cerebral-pathologic origin. Clinical and pathologic experiences of my own and other observers indicate that bilateral visual disorientation or visuospatial agnosia of the extent and nature as had obtained in his case usually results from bilateral cerebral disease involving both parietal lobes.

It would not be surprising that a patient with bilateral visual disorientation or visuo-spatial agnosia due to bilateral parietal or parieto-occipital disease, primarily affecting extrapersonal space but capable of encroaching upon personal space, should also prove to have some elements of what has been originally described by me as the syndrome of finger agnosia and its associated features, though usually concealed behind a more extensive or diffuse clinical picture, or else unrecognized as such. The converse does not occur, however, that is, a patient with the Gerstmann syndrome due to unilateral (dominant) parietal or parieto-

*Elaboration of this statement is prevented by limitation of space.

occipital lesion, complete or incomplete,† is usually not disoriented in outer space and does not show symptoms of visuo-spatial-agnostic (or visuo-psychic) disturbances as to position, distance, or directional, dimensional, and topographical relationships of objects outside the body and in various spatial manipulations.

I should like to close with a quotation from Critchley:[5] "On the face of it, the assembly of four unlikely or unexpected symptoms so as to constitute a clear-cut and frequently occurring syndrome is a matter of surprise." It was, at first, also a matter of surprise to me, until on the basis of numerous observations and case studies over many years and steadily increasing confirmations in the literature, the clear-cut existence and frequent occurrence of the clinical syndrome, its cerebral pathology, and its local diagnostic value, as well as the close functional interrelation and interaction of the four cardinal symptoms, have been firmly established. Critchley went on: "We can safely assume that neurologists, for generations, have been confronted with the syndrome without, however, realizing the fact. This is shown by such case reports as those of van Woerkom and of Bonhoeffer – and no doubt many others – which antedated Gerstmann's inspired observation."

†Benton and Meyers seem to question the neurologically recognized close association between the four cardinal features of the Gerstmann syndrome on account of "incomplete" forms of it recorded in the literature. First, one must always expect deviations from typical cases in any kind of a clinical-pathologic condition. Secondly, it is necessary to realize that incomplete cases in the literature "only too often indicate inadequate examination, or even ignorance of what to look for."[6]

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■ There are cases of very slight epileptic fits in which occurs what is commonly called an "intellectual aura;" I call it "dreamy state." One variety of it is the feeling of "reminiscence" which many healthy people have. Now, if with the "dreamy state" occurring suddenly, there be a "warning" of smell or of taste or a sensation referred to the epigastric region, there is certainly epilepsy; there is always defect of consciousness, but loss of consciousness does not always follow. These seizures are often so slight, so odd, so short, so little incapacitating, and are sometimes, strange to say, positively agreeable, that the patient may disregard them until a severe fit comes to tell him what they mean. Medical men, until the diagnosis is made by a severe, and, so to say, an ordinary fit, may not recognize the epileptic nature of these quasi-trifling seizures, and may put them down to hysteria, indigestion, malaria, etc. The diagnosis of slight fits of epilepsy from accounts given by patients or their friends is often so difficult that we cannot afford to neglect quasi-trifling symptoms. In some of the cases of the sub-variety of epilepsy just remarked on, there is very seldom a warning of taste, but there are not rarely movements and noise of chewing, or tasting, or smacking the lips, or there may be spitting, implying, I submit, discharge of central gustatory elements. If, with defect of consciousness and the "dreamy state," there are such movements, I should conclude confidently for epilepsy.

J. Hughlings Jackson in *Remarks on the Diagnosis and Treatment of Diseases of the Brain*, published in 1888.

CASE REPORT

Insulinoma Simulating Epilepsy

Thomas M. Runge, M.D., Joseph T. Gilbert, M.D., Charles F. Pelphrey, M.D. and H. R. Gaddy, Jr., M.D.

HYPERINSULINISM may be due to islet adenoma, carcinoma, or hyperplasia. The first case treated surgically was Graham's[1] in 1929. Since then over 400 cases have been reported, about 45 per cent at autopsy.

The clinical picture is that of episodes of fatigue, weakness, irritability, anxiety, tremor, sweating, circumoral numbness, palpitation, fainting, and even convulsions. The symptoms fluctuate in severity, tending to become more pronounced with time. Personality changes may be prominent and hysteria or psychosis suspected. The patient may become obese due to conscious or subconscious relief of symptoms with sugar.

In addition to hypoglycemic symptoms, certain neurologic phenomena may occur, including progressive muscular atrophy and neuronopathy. Several such cases have been reported with remission following surgical removal of islet cell adenoma.[2–6] Vasomotor symptoms, including tachycardia, palpitation, anxiety, and pallor, are thought to be related to increased adrenal output of epinephrine.[7] That increased adrenal output of epinephrine is a protective mechanism to elevate the falling blood sugar is suggested by the work of Gammon and Tenery,[8] who showed that adrenalin given parenterally will relieve the hypoglycemic symptoms in a patient suffering from hyperinsulinism.

The most comprehensive surgical and statistical review is that of Howard, Moss, and Rhoads,[9] who found in the world literature 398 patients with islet cell tumors, 37 of which were clinically and morphologically malignant. Of these 37 tumors, 22 caused hyperinsulinism and 15 were non-functioning. Of the remaining 361 localized tumors, 161 were found only at autopsy. Multiple adenomas were found in 12.6 per cent of cases, while ectopic pancreatic tissue was present in nine patients.

In addition to islet cell adenomas and carcinomas, hyperplasia of the islet cells (based upon the number and/or size of the islets) may produce the same clinical picture. Diffuse islet hyperplasia may also accompany islet cell tumor.[10]

Adenomatosis of the islets with numerous small insulin producing adenomas has been reported by Bickerstaff, Dodge, Gourevitch, and Hearn.[11]

PATHOGENESIS

While the pathogenesis of the adenomas is unknown, Breidahl, Priestley, and Rynearson[12] have reported the condition associated with a family history of diabetes in 24 per cent of cases, as contrasted with an average 3 to 6 per cent family history of diabetes in the general population.[13]

DIAGNOSIS

Hyperinsulinism must be distinguished from the very common functional hypoglycemias. The former is associated with 1) blood sugar values of 50 mg. or less, 2) occurrence of episodes while fasting, and 3) relief of episodes by glucose (triad of Whipple). On the other hand, functional hypoglycemia occurs about two hours after eating, usually is not seen after an overnight fast, and is not associated with such marked symptoms or such marked reduction in blood sugar.

CASE REPORT

A 58 year old married woman was seen on November 5, 1956 complaining of "epilepsy." Onset of symptoms occurred eight years previously, with episodes of anxiety, hyperpnea, sweating, and paresthesia of the hands, feet and circumoral region. More severe episodes with tremor, aphasia, falling, and syncope were described, lasting as long as an hour, but were not associated with tongue biting or urinary incontinence. Occasionally uncontrollable screaming occurred. Complete relief of symptoms had never been obtained, but some benefit from Dilantin and phenobarbital was noted.

The patient had had a weight gain of 15 pounds in the past year, and showed irritability and emotional instability. The history indicated a brief episode of diplopia several years previously, mild nocturia, chronic constipation, occasional difficulty initiating urination, and hot flashes for eight years.

Dr. Runge: Capital National Bank Building, Austin, Texas.

TABLE 1

PREOPERATIVE FASTING BLOOD SUGARS, INSULIN TOLERANCE TEST, AND GLUCOSE TOLERANCE TEST. POSTOPERATIVE FASTING BLOOD SUGARS

Fasting blood sugar

Preoperative	Postoperative
58, 72, 84, 40 mg.%	189, 146, 129 mg.%

Insulin tolerance test

1:00 p.m.—69 mg.%; 2:25 p.m.—43 mg.%

Glucose tolerance test

Blood sugar	Urine sugar
F.B.S.—45 mg.%	Negative
½ hr.—133 mg.%	Negative
1 hr.— 90 mg.%	Negative
2 hr.— 58 mg.%	Negative
3 hr.— 64 mg.%	Negative

She had undergone a cholecystostomy and surgery for benign rectal tumor and benign tumor of the breast.

The family history revealed the death of her father at 70 of a stroke; a brother was diabetic.

Physical examination: The patient was an unhappy, pale, 125 pound, 58 year old white female, 5′ 7″ tall; pulse was 84, temperature 98.2, and blood pressure 160/105 left arm. There was no bruit over the skull, the optic fundi revealed grade II (Keith and Wagener) arteriolar changes. The right breast was amputated, and there was mild intracutaneous edema of the ankles. The skin was dark (but had always been so).

The remainder of the general physical examination was not remarkable, and the complete neurologic examination was within normal limits, though tendon reflexes were slightly more active in the arms than legs. Fasting blood sugar was 66 mg. per cent.

After physical examination the patient was pale and sweating, and she was questioned as to whether or not she was having one of her episodes. She stated she was not, but that she was angry because she had been subjected to such a prolonged examination. At this point another blood sugar value was 59 mg. per cent. She remained antagonistic and declined hospitalization. Later, after encouragement from her family physician, she consented to hospitalization.

The electroencephalogram was within normal limits, revealing generalized eight to ten per second 20 to 30 mv. activity, with no significant change following hyperventilation. For a resume of the pertinent laboratory data see table 1.

In the hospital she had two episodes which she classified as mild, with profuse sweating and marked tremor of the arms and legs. One of these occurred in the x-ray department and alarmed the staff who administered oxygen, but a blood sugar was not obtained. The other episode occurred also after a prolonged overnight fast and blood sugar during this episode was 40 mg. per cent. Fasting blood sugars were taken on several mornings and, while two values were over 80 (84 and 87), the remainder were under 80 (45, 58, and 72). The insulin tolerance test suggested normal responsiveness to insulin; however, it is possible that the patient was having a spontaneous hypoglycemic episode at this time.

Although the triad of Whipple was not complete due to failure to give glucose during an episode, we felt the clinical picture plus the blood sugar of 40 mg. per cent striking enough to warrant exploration.

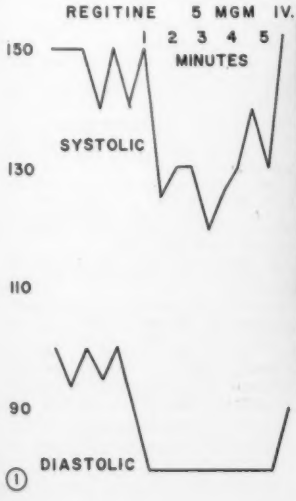

FIG. 1. Intravenous Regitine test preoperatively.
FIG. 2. Photograph taken at surgery showing insulinoma at left and just to right of this, small accessory spleen.

The response to phentolamine (figure 1) intravenously caused consideration of the coexistence of pheochromocytoma, a fall to normotension (120/80) being attained.

At surgery the pancreas was quite mobile and a well demarcated globular purple-red tumor weighing 5.5 gm. and measuring 2.3 by 2.6 cm. was found in the tail of the pancreas (figure 2). Microscopically this was benign and was demonstrated to be pure islet tissue. Bioassay in a rabbit, using 20 per cent of an extract of 1 gm. of tumor tissue injected intraperitoneally, resulted in a blood sugar reduction of 44 mg. per cent in 45 minutes (fasting 132; 45 min. 88 mg. per cent; 80 min. 112 mg. per cent). A portion of attached pancreas purposely removed for frozen and permanent section was normal as to islet size and distribution. The gallbladder containing stones was also removed, as was the normal appendix.

The postoperative course was uneventful, except for gaseous distention for several days and rebound elevation in blood sugar to 189 (first postoperative day), 146 (second postoperative day), and 129 mg. per cent (fifth postoperative day). Subsequently, the patient became asymptomatic.

COMMENT

The patient's most prominent symptoms were episodes suggesting seizures which were benefited by Dilantin and phenobarbital. Her preoperative personality was one of chronic irritability and mild depression, punctuated by severe hypoglycemic episodes. Postoperatively she has had no episodes and her day-to-day personality is more placid.

Of interest is the drop in blood pressure from 150/100 to 120/80 after giving the adrenolytic agent phentolamine (Regitine). Strictly interpreted, this is not a diagnostic reduction for pheochromocytoma (35 systolic and 25 diastolic advised) but is greater than we usually see in essential hypertension and also represents a decline to completely normotensive levels. Clinically, insulinoma and pheochromocytoma have many symptoms in common.

That part of the symptomatology of insulinoma may be due to reflex overproduction of adrenalin has been suggested by others,[7] and is probably a protective mechanism, that is, excessive adrenalin output to correct hypoglycemia through mobilization of liver glycogen.

False positive Regitine tests have been reported in uremia and in patients who have received sedatives, narcotics, and antihypertensive agents (Apresoline). They are also known to occur rarely for unexplained causes, and it is recommended that a single test not be relied upon. False positives are said to occur more often with the intravenous route than with the intramuscular route. As with other drugs, indications for the test should be realistic, since at least one fatality has been reported.[14]

SUMMARY

A case of hyperinsulinism simulating epilepsy is reported. The possibility of confusion with pheochromocytoma both clinically and from laboratory studies (Regitine test) is mentioned.

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CASE REPORT

Hemiballismus Secondary to Metastatic Carcinoma of the Gall Bladder

Lloyd J. Lemmen, M.D., James S. Davis, M.D. and Edwin R. Fisher, M.D.

HEMIBALLISMUS presents a type of involuntary movement which may result from a lesion in the contralateral subthalamic nucleus or its anatomic connecting pathways. Information about this phenomenon remains incomplete with regard to etiologic factors, site of the lesion, and therapy. It has been observed in a patient who had gall bladder carcinoma with a metastatic tumor nodule in the region of the subthalamic nucleus.

CASE REPORT

A 59-year-old white male experienced involuntary movement of the right arm for one month. This developed suddenly while he was shoveling coal into a furnace. Slight uncontrolled activity in the right leg was noted by his wife during the week prior to hospital admission.

When first examined the patient was oriented, cooperative, and without aphasia. Recurrent, gross, purposeless "throwing" motion of the right arm, shoulder, and hand accompanied by facial grimacing was evident. The patient could stop these activities voluntarily for only 30 seconds. These abnormal movements would begin in a similar length of time if the extremity was externally restrained. An occasional kicking motion occurred in the right leg. No abnormal involuntary activity was noted in the glossal or deglutitional musculature. He was able to walk and had his usual strength in all extremities. Deep tendon reflexes could not be evaluated in the right upper extremity. Normal plantar responses were present. The optic disks were normal. Sensation was intact. The blood pressure was 156/80 mm. Hg. General physical examination disclosed no abnormalities.

Laboratory studies including urinalysis, complete blood count, and a serologic test for syphilis were within normal limits. The prothrombin time was 15 seconds, as compared to 13 seconds for a control. Blood chemistry determinations revealed a total serum protein of 6.1 gm. per cent, albumin 3.1 gm. per cent, globulin 3.0 gm. per cent, serum bilirubin 0.84 mg. per cent, van den Bergh direct –0, indirect –0.84, cephalin flocculation negative at 24 and 48 hours, thymol turbidity 1.0 units, CO_2 combining power of 54 vol. per cent, serum sodium 148 m.e.q./l., potassium 4.7 m.e.q./l., and serum chlorides 107 m.e.q./l. Chest and skull roentgenograms were normal.

Following admission to the hospital the patient was quite restless and the bizarre movements continued. Four days after admission it was noted that the movements in the right arm and leg stopped while the patient was asleep but resumed when he awoke. Subsequently he became confused, his speech became explosive, and he had outbursts of animal-like cries. The oral or intramuscular administration of 0.45 gm. Nembutal every four hours resulted in somnolence and almost complete cessation of the involuntary movements. He was given 0.25 gm. reserpine four times a day orally for one week without inducing any change in the abnormal activities. The substitution of 25 mg. chlorpromazine orally three times a day and 250 mg. zoxazolamine three times a day produced no change in the movements. Eight days before death he experienced melena for a 48-hour period, and three days later had coffee ground emesis and became unresponsive. Involuntary movements of the right upper extremity persisted until shortly before death.

Autopsy examination disclosed a polypoid adenocarcinoma of the fundus of the gall bladder. Microscopically, it was characterized by atypical glands with frequent reduplication of lumens. The tumor cells were pleomorphic and for the most part columnar. The cytoplasm was faintly acidophilic and the nuclei were vesicular as well as hyperchromatic and irregular. Mitoses including atypical forms were frequently evident. A relatively acellular connective tissue stroma was observed coursing through the neoplasm. The origin of the neoplasm from the mucous membrane of the gall bladder was evident from the dysplastic change observed in adjacent mucosal epithelium. The tumor appeared confined within the musuclar coats of the gall bladder, although lymphatic and venous extensions were apparent.

Similar appearing neoplasm was evident in periportal lymph nodes, liver, and brain.

The brain weighed 1300 gm. and was of normal configuration. Minimal atherosclerosis was apparent in the basilar artery. Coronal sections revealed a metastatic tumor nodule, measuring 3 by 2 by 1 cm. in the left ventral thalamus. Another tumor nodule was present in the right frontoparietal area, meas-

From the surgical and laboratory services, Veterans Administration Hospital, and University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

Read by title at the ninth annual meeting of the American Academy of Neurology, April 1957, Boston, Massachusetts.

uring 2.5 cm. in cross diameter. Microscopically these were morphologically identical to the neoplasm observed within the gall bladder and the other metastatic sites. The neoplasm involved the lateral portion of the ventral thalamus, the medial border of the substantia nigra, the adjacent ventrolateral portion of the dorsal thalamus, posterior limb of the internal capsule, and the more caudal-medial portions of the lentiform nucleus. The neoplasm extended caudad in the substance of the subthalamic nucleus, and appeared to replace its entire length. Sections from uninvolved areas of the brain revealed moderate edema and focal perivascular lymphocytic infiltration.

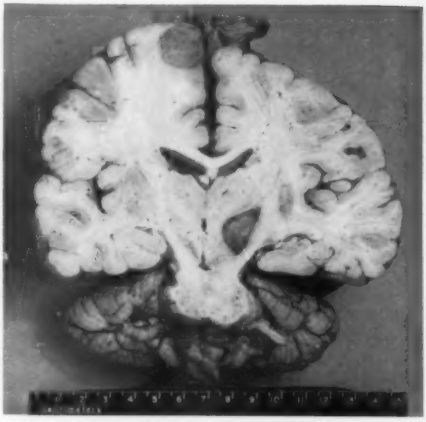

FIG. 1. Photograph of coronal section of the brain, demonstrating the metastatic tumor from the gall bladder in the left ventral thalamus and right frontoparietal area.

DISCUSSION

Hemiballismus resulting from metastatic neoplasms in the subthalamic region has been reported most frequently from a primary breast tumor. Pette[1] reported such a case in which a severe choreiform disturbance of the whole left side of the body resulted from a pea-sized neoplastic metastasis in the subthalamic region. Bremme[2] and Bonhoeffer[3] each described a lesion which involved the subthalamic nucleus and substantia nigra. In the former case there was an involvement of the internal capsule and lenticular fasciculus, while a breast metastasis involved the thalamic fasciculus (H_1) in the latter case. Kelman[4] observed hemiballism when a small metastatic carcinoma from the lung involved the tip of the oral pole of the subthalamic nucleus and afferent subthalamic tegmental fibers. The case here presented is of interest in that the patient's initial complaints were due to central nervous system involvement. Not until necropsy examination were the metastases from a primary carcinoma of the gall bladder demonstrated. The presence of occult carcinoma of the gall bladder has been reported previously.[5] Involvement of the contralateral subthalamic region by metastatic lesion from the gall bladder in this case correlates with the symptoms of hemiballism; Whittier's[6] study showed that this was the inevitable symptom in man of a destructive lesion in the contralateral subthalamic nucleus. Precise localization of hemiballism to destruction of the subthalamic nucleus cannot be made in this case, since neoplasm involved adjacent structures and the right frontoparietal area.

The precipitous onset of symptoms would not be anticipated in a neoplastic lesion. These movements stopped during sleep, were decreased by heavy sedation, and were not affected by reserpine, chlorpromazine, and zoxazolamine. Attempts at alleviation of the hemiballism by complete or partial interruption of pyramidal or extrapyramidal systems would have been of limited value in this case.

SUMMARY

The presenting findings of hemiballism were observed in a case which at autopsy revealed a carcinoma of the gall bladder with metastases to the contralateral subthalamic nucleus. Reserpine, chlorpromazine, and zoxazolamine had no effect on the involuntary movements.

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Neurology

BOOK REVIEWS

Basal Vascular Disease

Die vaskulären Erkrankungen im Gebiet der Arteria vertebralis und Arteria basialis. Eine anatomische und pathologische, klinische und neuroradiologische Studie. H. Krayenbühl and M. G. Yasargil, Neurochirurgischen Universitätsklinik Zürich. 1957. Stuttgart: G. Thieme. (Intercontinental Medical Book Corporation, New York, 14, N. Y.). 170 pages. $18.35.

WITHOUT DOUBT, an encyclopedic monograph on a limited subject is most valuable for a specialist working in that general field. The neurologist will find this treatise on the diseases of the vertebral and basilar arteries to be such a text. The study is based upon an analysis of 250 vertebral and 500 carotid angiograms, 200 roentgenograms of the cervical spine, 400 autopsy specimens, and 15 brains having the vessels specially injected. Although this voluminous material has served as a basis for the work, the pertinent literature is utilized frequently to amplify and complement the authors' own findings.

After a brief review of the embryology of the basilar vessels, largely based upon the works of Streeter and Mrs. Padget, the authors present diagrammatically the normal and variations in the topographic anatomy of the vertebral and basilar arteries. The distribution of the branches of these vessels in the brainstem is shown by sketches and photographs. The clinical symptomatology produced by their occlusion is discussed with reference to the many pathologic syndromes reported in the literature of the past century.

The best parts of the book are found in the last half, in which the authors present the angiographic findings of the vertebral and basilar arteries in normal and diseased states. The normal variations of the major vessels and their branches are well shown in reproductions of angiograms and line drawings copied from the roentgenograms. Pathologic alterations of the vessels – occlusion, narrowing, aneurysmal dilatation, malformations, and neoplasms – are all depicted in excellent illustrations and discussed in the light of the literature on the subject.

The references grouped as to subject cover the English, American, French, and German literature quite thoroughly.

Although the monograph is in German, it is so profusely illustrated that anyone with a slight knowledge of the language should have no trouble reading it. Perhaps its most conspicuous shortcoming is the absence of a discussion of the gross and microscopic pathologic anatomy. In other respects the authors have covered the subject well, particularly their special interest – namely, angiographic demonstrations of the vessels at the base of the brain in health and disease.

The monograph is well composed and contains many beautifully reproduced angiograms. It can be recommended to all students of the nervous system who wish to delve seriously into the problems of the blood supply of the base of the brain. Neurologists, in general, should find it a very helpful reference book.

A. E. W.

The Medical Interview

Aineslie Meares. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 117 pages, $3.50.

THIS SMALL VOLUME has been written not for medical students who are well trained in the art of interviewing nor for psychiatrists in training. Rather it has been designed to aid the general practitioner, a large part of whose time is taken up in interviewing patients who do not have organic illness.

Although the relative numbers of trained psychiatrists have increased, there still remains a shortage of these specialists to stem the ris-

ing tide of mental illness. Not all patients with non-organic illness need to be or should be referred to psychiatrists. With a little insight into the technic of interviewing and knowledge of simple dynamic mechanisms of behavior, the general practitioner and medical and surgical specialists can select the more seriously disturbed for referral to the psychiatrists. The majority can be helped and will be grateful to the doctor they have chosen to consult for their somatic complaints.

There is no gobbledygook language to discourage the reader of this little book. The language is simple and the approach direct. The author discusses briefly such subjects as motivation in the patient in the interview and motivation in the physician necessary for the medical interview to be a therapeutic success. It discusses what takes place psychologically in the patient and the physician during the interview. The dynamics of extra and non-verbal communication, the meaning of patient hostility, as well as hostility engendered in physicians by some patients, are touched upon. Suggestions are made for handling hostility.

A chapter is devoted to the emotional nature of rapport, the technics of establishing a comfortable relationship between the subject and his physician. The role of the physical examination is stressed, not alone for the assessment of the patient's complaints but for the psychologic effect in establishing better rapport. It is pointed out that this increases the prestige of the physician in the mind of the patient and often has the further effect of uncovering data the patient has held back as he was furtively evaluating the sensitivity of the physician.

The implications of this primer for office practice are that any practitioner with a real desire to understand and help his patients can do so without full insight into their psychopathology. It is well known in psychiatric circles that so-called depth insight by the patient, which is the object of psychoanalysis, does not always cure his symptoms.

There is great reward to the physician who learns after a series of interviews, sometimes in a single conference, that his patient is over the hump, again master of his doubts and fears of disease and death. The reading of this simple text will sharpen the physician's insight into psychologic factors of the medical interview and stimulate his efforts to using it as a therapeutic tool.

M. G. M.

Therapeutic Exercises for the Treatment of the Neurologically Disabled: a Text for Corrective Therapists and Corrective Physical Educators

Harold J. Brenner. 1957. Springfield, Illinois: Charles C Thomas, Publisher. 84 pages. $3.50.

PHYSICAL EDUCATORS specializing in the rehabilitation of the physically handicapped or mentally ill are known as corrective therapists. This book is written from the point of view of a corrective therapist working as a part of a medical rehabilitation team.

The first chapter touches the development and philosophy of rehabilitation through corrective exercises. Therapeutic exercises and ambulation procedures are simply and clearly described in the following two chapters. Five short individual chapters describe the application of corrective exercises to specific neurologic disabilities: hemiplegia, multiple sclerosis, parkinsonism, poliomyelitis, and polyneuritis. Each chapter discusses simply and clearly the history and etiology, symptoms, prognosis, corrective treatment, and goals or objectives. The bibiliography is adequate and a glossary of terms is appended. Illustrations of procedures and apparatus are good.

This book was written by a corrective therapist for other corrective therapists, corrective physical educators, and college students. With this in mind, one must compliment the author on the simple, brief, accurate descriptions of neurologic syndromes. The book is recommended for physicians who desire an introduction to the application of corrective exercises for the rehabilitation of neurologically disabled patients.

J. R. B.

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GRADUATE TRAINING GRANTS

The Surgeon General of the Public Health Service, upon recommendation of the National Advisory Neurological Diseases and Blindness Council, may make grants of funds to public and private institutions providing postdoctoral training in areas encompassing neurologic and sensory disorders. The purpose of such grants is to help training institutions to increase the number of personnel especially trained for academic careers as teachers and investigators in areas of special need.

This Conference on Graduate Training in Clinical Neurology—the second of its kind—is dedicated to reviewing the progress made in training over the past year, to consider the problems that have arisen in conjunction with such training, and to offer recommendations for further development and improvement.

Chairman's Remarks

A. L. Sahs, M.D.

MEMBERS of the Conference on Graduate Training in Clinical Neurology: It is with pleasure that I call this group together in the first general session. Your presence is ample evidence of your interest in the important subject of graduate training. The atmosphere of optimism and the opportunities for the sampling of opinion will make this conference a most successful one. Although complete agreement is not to be expected in all matters, we hope that through your assistance and advice we may record and eventually publish the substance of this meeting.

It is imperative at this time that leading neurologists meet in an atmosphere conducive to free expression of individual opinion, in order to establish the major policies which will define the scope and objectives of their specialty and to outline the conditions under which that specialty will be most productive and able to provide the greatest possible service.

One must take cognizance of the renaissance of neurology. Up to one decade ago the rapid decline and early demise of this specialty was predicted freely and openly. This attitude of gloom and foreboding was shared by some of our colleagues within the field. There is growing evidence that we have escaped such a dire fate. The recently concluded meeting of the American Academy of Neurology in Boston and the enthusiastic participation of young men in its activities are ample evidence of the expansion within the specialty. The fact that American neurology is assuming its rightful place in the international picture is further evidence that the specialty is assuming obligations which are associated with maturity and broadness of outlook. Requests for service coverage are multiplying. Increasing demands for highly trained neurologists are being received from medical schools, clinics, the Veterans Administration, voluntary health organizations, and others. Activities in teaching and research have been stimulated noticeably. Energetic and enthusiastic young men are being attracted to a field which has expanded beyond the limited confines of routine clinical diagnosis and a very limited therapeutic program, to a revitalized specialty which is attacking the problems of neurologic disease with new technics and renewed vigor.

Credit must be given to all those who have contributed so generously of their time and energy to make this meeting possible. We are particularly grateful to Dr. Pearce Bailey and Dr. Gordon Seger of the National Institute of Neurological Diseases and Blindness for their generous support.

At this first general session we will hear Doctor Baker's paper on the early history of the training grant program, and Dr. Seger will review matters of administration of the training grant program in neurology. Tomorrow you will be assigned to small groups, each with a chairman, to study such problems as clinical aspects of training in neurology, basic science aspects of training in neurology, and administrative aspects of training in neurology. Reports of the panel chairmen will be heard in the second general session on the following day.

Professor and head of the department of neurology, State University of Iowa, Iowa City, Iowa. Chairman of the Neurology Training Grant Committee of the National Institute of Neurological Diseases and Blindness.

Early History of the Training Grant Program

A. B. Baker, M.D.

IT IS MY PRIVILEGE to address you at this most important second conference on neurologic education sponsored by the National Institute of Neurological Diseases and Blindness. It is an occasion that I readily welcome, since it affords me an opportunity of outlining to you some of the many problems, some of the really difficult decisions, and some of the effort and hard work encountered in developing and expanding graduate neurologic training in the United States. Many of you were perhaps uneasy and unhappy with some of the steps taken in developing a national program. It is also possible that some of us on the committee lost a number of friends because of recommendations and actions that were not entirely in accord with your views and feelings. I can assure you, however, that every recommendation of the committee was motivated sincerely and unselfishly by the goal of helping neurology develop strongly in this country and with a purpose of establishing a really sound training program in this specialty.

I should like to take a few moments to review briefly the development of the training grant program of the National Institute of Neurological Diseases and Blindness since, in my opinion, it actually indicates the progress made in neurology in this country. Five years ago, in 1952, when I was first asked to accept the chairmanship of the newly created training grant program in neurology, conditions in this field were far from optimistic. It is true that there were some very active and strong neurologic training programs scattered throughout the country, but these were relatively few in number and were concentrated mostly in the East and Midwest. Actually, there was no real demand for such training centers or for expansion of such programs. This lack of interest in graduate neurologic education could be related directly to the general lack of interest in neurology in the medical schools and to the lack of public information regarding neurology and neurologic illnesses. For example, in 1952 of the 79 medical schools in this country only 15 had training programs in clinical neurology, with only 90 residents in training. Actually there were only about 250 qualified neurologists in the United States and six states did not have a single board certified neurologist. For certain areas of the South, there was only a single neurologist for almost a million patient population. Even more disturbing was the fact that, of some 7500 physicians graduated each year from our medical schools, less than 50 per cent received an organized course in neurology given by a neurologist so that they might be able to recognize neurologic illnesses or apply the known treatment procedures in this field. This lack of proper student exposure had two very alarming effects: 1) it deprived the public of the benefits of known therapies even when treatment was available, and 2) it deprived over half of the graduating physicians from exposure and subsequent interest in neurology, thus reducing the possible teaching and research interest in this field. Even more distressing was the fact that many of our own colleagues in neurology had accepted the fatalistic viewpoint that it was impossible to "make a living" in neurology and hence discouraged young men from entering the field.

In striking contrast to this unhappy professional picture was the tremendous and unbelievable patient load. In this country there were at that time and still are over 15 million individuals disabled by neurologic and sensory disorders, almost twice the number of people suffering from heart disease and cancer combined. This figure does not include the many patients suffering from acute neurologic illnesses or any of the patients presenting themselves to physicians with neurologic symptoms or neurologic complications of internal disease. It seemed hard to understand why, with such a large patient load in the neurologic field, the medical profession generally and neurologists in particular should have been so pessimistic about the future of this specialty and the need to expand training in this field.

The impetus to do something about this problem did not come from the medical profession or from those of us in the neurologic specialty. We can take very little credit for

Professor and director of the neurology division, University of Minnesota Medical School, Minneapolis, Minnesota. Chairman of the Neurology Graduate Training Grant Committee, September 1953 to December 1956.

what has occurred in this field. The patients themselves were responsible for the move to solve this unhappy and critical problem. They issued a mandate to their voluntary health groups to cooperate and to attempt to stimulate interest in developing more medical talent dealing with diseases of the nervous system. This mandate was issued two years after the Federal Government had established the National Institute of Neurological Diseases and Blindness but had not seen fit to supply an adequate budget to support training or research in this field. I should like to point out that one could not blame Congress for this lack of interest in neurology and neurologic illnesses. It was in part the fault of the profession itself, and of many of us here in the audience as well. The professional neurologic groups had not considered it important enough to acquaint Congress and the public with the magnitude and importance of neurologic problems in this country. It was this lack of public education and information that was being reflected in the status of neurology and neurologic education in medical schools throughout the country where neurologic teaching was generally at a low ebb. As a result of this mandate by the people in 1952, six of the voluntary health groups interested in neurology, namely, American League Aganist Epilepsy, United Cerebral Palsy Associations, Committee for Public Understanding of Epilepsy, National Multiple Sclerosis Society, Muscular Dystrophy Association, and National Society for Crippled Children and Adults, formed the National Committee for Research in Neurologic Disorders. The most important first step in the activities of this committee was to appoint a subcommittee on public education to create a greater public awareness of the needs of the many sufferers of crippling neurologic disorders and, thus, to obtain more congressional support for research and teaching in this field. I wonder how many of you in the field were, or even now are, acquainted with the tremendous and courageous job done by the National Committee for Research in Neurological Disorders. As a result of these efforts, Congress in 1953 for the first time appropriated funds to the National Institute of Neurological Diseases and Blindness to be used for training grants. The availability of these funds resulted in the establishment of the Neurology Graduate Training Grant Committee to advise the Public Health Service, through the National Advisory Neurological Diseases and Blindness Council, on the establishment, expansion, and maintenance of an adequate program of training in neurology.

Those of us who were asked to serve on this first committee realized that we had accepted a tremendous responsibility to the entire field of neurology. Only with proper development of this training program would it be possible to stimulate increasing numbers of physicians to enter the field of teaching and research in neurology; only by proper development of such a program would it be possible to supply the specialists necessary to initiate additional neurologic programs in schools that had no such programs; only by the development of strong neurology programs in medical schools would it be possible to offer graduating physicians the type of neurologic orientation that would enable them to diagnose and treat these illnesses properly in their patients, and stimulate in many of them a desire to study and investigate such illnesses; and only by the proper growth of such a program could one expect to obtain additional support from Congress to continue the expansion of this most important phase of medical education. With no previous protocols or experiences to be used as guides, the Neurology Training Grant Committee had to make decisions carefully.

Obviously, the first decision that faced the committee was how to spend the limited funds available in order to produce the maximum benefit and growth of the program. I should like to emphasize once again that throughout the deliberations of this committee the prime consideration in all its decisions was the "specialty of neurology" and how to improve this phase of medicine in our country. This was and I hope will continue at all times to be the goal of this particular committee. From a survey of the neurologic problem, it was apparent that the single greatest need was for more well trained neurologic teachers. In view of the dearth of such specialists, it seemed impossible to initiate new programs or expand research facilities. It was decided to begin the program by implementing the already established training programs in neurology, so that with additional staff and equipment they could increase the number of their trainees. These established programs were not finding it too difficult to obtain trainees and such expansion was thought to be feasible. Although this was the main effort of the committee, a number of new training programs were supported in those institutions where personnel was available and interest was expressed in such training. At the committee's

first meeting, therefore, funds were made available for the implementation of nine well established programs. In addition, funds were allotted to five schools to begin new programs —all these schools having available a well trained neurologist to act as program director. In five schools applying for funds, the committee deferred action since it felt that not enough information was available to decide whether a new program in neurology was feasible or had even the slightest chance of success.

These latter situations produced the need for the second main decision of the committee, a decision that I am sure has impressed (either positively or negatively) many of you present here. The information obtained from an applicant for training funds was often inadequate to formulate proper opinion concerning the potential of the program available or planned. In most of their original decisions, the committee members were well enough acquainted with the training programs or schools to be able to offer personal knowledge in arriving at a recommendation. However, in order to avoid the error of doing an injustice to an applicant merely because inadequate information was available, it was felt that it would be wise to establish a policy of requiring a program site visit to an institution before any new or renewal grants were recommended. Such visits by members of the committee would enable them to advise a new program director in the submission of his application or in the organization of his program if such help were needed. It would also help established programs by explaining how funds could be utilized within training grant policy and by reemphasizing the purpose and aims of the training program. It was realized that such a decision was a formidable one since, as the program grew, it would tax the time and effort of every committee member and would require constant sacrifice of time and neglect of one's own activities. The committee did not underestimate that portion of the program. The rapid growth of the program has indeed taxed the time of all the committee members. I should like to take this opportunity to thank the members of the committee while I was chairman for their unlimited generosity with their time in making these visits. None of the members was ever too busy to accept another visiting job, but I am sure a number of medical schools began to wonder what had happened to their professors of neurology because of frequent absences.

In spite of the effort involved, this phase of the committee's activities was very helpful in the establishment of a sound program. It enabled the committee to recommend the award of funds on the merits of a program determined by personal observations. It enabled the committee to assist new program directors in the development and expansion of their programs. It gave medical school faculties and deans an opportunity periodically to discuss needs and development of neurologic education in their schools and to benefit from the experience of those active in this field. I am sure it has stimulated interest in neurologic education in many new areas. I hope many of you here who have new programs feel that you have benefited from such visits.

I should like to emphasize still other factors in the evaluation of training grant applications. Often when certain requests are not recommended following a program site visit, the visitors or the chairman of the committee are considered personally responsible for this action. The viewpoints of the program site visitors are taken into consideration, but the final recommendation represents the opinion of the committee as a whole. This recommendation is then considered by the National Advisory Neurological Diseases and Blindness Council. This multiple review assures objectivity and impartiality.

Still another factor was taken into consideration by the committee. This involved the length of commitment of training grant funds. It was believed that commitment of funds for long periods of time made for stability and made it easier to acquire teaching personnel. Therefore, in all established programs in which the committee was confident of the caliber of training to be given, commitments were recommended for periods of five years. However, it was felt that this might be an unwise procedure in newer programs where there was uncertainty about the ability of the program director or the academic status of neurology in the institution. It was felt that it might be wiser in such programs to recommend the initial grant for a shorter period of time and, if the program developed adequately, to urge that the renewal grant be for a longer period. Such a procedure then avoided the danger of tying up the limited funds available at institutions where programs were not developing adequately even after funds had been made available. The justification of this procedure can be shown by the fact that a few of the training programs that were awarded grants

early when funds were not too plentiful have not as yet begun to develop their programs, have not acquired program directors, and have failed to use the funds committed.

Since the onset of the training grants program of the National Institute of Neurological Diseases and Blindness, expansion of neurologic training has advanced very rapidly. Through the continued effort of the National Committee for Research in Neurologic Disorders and other interested organizations, a magnificent job has been done in convincing Congress of the importance of neurologic education. As a result, Congress has responded liberally with large increases in the Institute budget specifically earmarked for training. Within a period of four years the training grant budget increased from $36,000 to $4,150,000. Naturally, this tremendous increase has been accompanied by a corresponding increase in the activities of the Neurology Training Grant Committee. From the meager beginning of supporting nine established and five new programs in neurology, the training grants program at the present time supports 45 programs, 16 of which are well established ones and 29 are new. This latter group of newly established programs really points to the tremendous progress made in neurology and neurologic education in America under the stimulus of the National Institute of Neurological Diseases and Blindness. In 29 schools and institutions new training programs have been instituted so as to increase the number of teachers and researchers in neurology. This increase is spread throughout the country, with 13 in the East, seven in the South, six in the West, and eight in the Midwest. The impact of this development is mirrored in the increase in neurologic residents from 90 in 1952 to over 200 in 1956.

With the rapid development in the training of clinical teachers and researchers in neurology, it was inevitable that this program should expand into the basic fields of neurology. Such a training program in basic neurologic sciences has been instituted and developed just within the past year. Its purpose is to develop more teachers and researchers in such basic fields as neurochemistry and neuropharmacology and to strengthen basic teaching so as to complement clinical training. I am sure Dr. Seger will have some comments to make concerning this program sometime during this conference. I feel certain that this basic program will prove most valuable in neurologic education.

One final comment on the activities of the Neurology Training Grant Committee. As the various programs developed and grants came up for renewal, a very important problem arose. How does one evaluate a training program? It was accepted that programs differed one from another, depending upon the facilities, the personnel, and the philosophy of the school and the program director. These differences made it difficult for the committee to establish a set of rules or a yardstick by which progress and accomplishments could be evaluated. However, if one keeps in mind that the entire program was instituted to obtain for the country more teachers and investigators in neurology, then the evaluation of a program can be quite specific. One merely has to determine how many individuals were trained to be teachers or investigators in neurology and survey the careers they select after such training. May I emphasize this point. The productivity of training programs in clinical neurology cannot be judged by the number of foreign physicians trained or by the number of internists, pediatricians, psychiatrists, and neurosurgeons given a few months of training, but simply and specifically by the number of teachers and investigators fully trained in clinical neurology as specialists in this field. The committee accepted this as one of the most important guides to progress in the training program. One other criterion was used, particularly in the new programs. It was apparent early that a neurologic program in a school would not be successful unless it had the support of the school's administration. It was felt that one of the best measures of such support was the degree to which the school was willing to help finance the program from its own funds once the program was established. After a program has been active for many years, it is an unhealthy sign if all the support, including staff salaries and operating expenses, still depends upon a grant from the Public Health Service. The least the school can do is offer token support to the program from its own funds as an indication of its interest and belief that clinical neurology is an essential part of medical education.

Finally, as the training grant program expanded, it became obvious to the committee that there was a very wide difference of opinion in regard to the method, content, facilities, and general philosophy of training in neurology. It was thought desirable to call the program directors together in order to discuss the various phases of neurologic education, with the hope that some common meeting of the minds might evolve. This is particularly im-

portant at a time when new programs are developing, many of which can use some guidance. The first conference was held one year ago to enable the various program directors to become better acquainted with one another, to outline the administrative aspects of the program, and to acquaint institutions with the goals of this training program.

Today we meet for an entirely different and more important purpose. It is to engage in a detailed and personal discussion of all aspects of neurologic education. At this point in the development of neurologic education, it is imperative that each of us disregard fixed ideas, tradition, and rigid principles and attempt to discuss honestly and liberally the problem of neurologic education and its effects on our country today, particularly in view of the rapidly increasing and continuing interest in this field. Neurologic education must be modified in accordance with the increasing demand for clinical neurologists to care for the 15 million disabled neurologic patients, with the increasing need for teachers and investigators in medical schools, and with new methods in teaching and research. The increased interest shown by various medical schools and other training institutions and the emergence of neurology as a dynamic phase of medicine have produced a demand so vast in its scope that it has required a rapid increase in the number of specialists in the field.

For these reasons it is important that all of us lay aside our own pet ideas for the next few days at least, and attempt in an open constructive discussion to evolve some guiding principles and plans for neurologic education that are acceptable to all of us interested in this field—principles that might be used as a guide for new programs that are and will be developing and for those schools which might be interested in what the neurologists themselves think of neurologic education. All of you will agree that this is the only sensible approach to this problem. May I warn you that the importance of these sessions must not be taken lightly by any of us here. We have a great responsibility to the neurologic field. If we as neurologists do not arrive at a set of principles and concepts for neurologic training acceptable to us, then such principles and concepts will continue to be made by others in the field of medicine less well equipped to do so. For too long a time neurologists have allowed others to speak and plan for them. The results of your deliberations at this point are vitally needed for the continued successful functioning of the training grant program in neurology. I trust that all of you here will put neurology first and foremost in your thinking and strive to benefit our specialty by your efforts at this conference.

Before closing, may I take this opportunity to thank Dr. Pearce Bailey for the guidance and counsel he has given me as chairman of the Neurology Graduate Training Grant Committee. It was a privilege working for and with him. Very few of us realize the tremendous effort he has exerted for the benefit of neurology. He is able to go about his work in a quiet, unassuming fashion which hides the greatness of his contribution. American neurology will forever be indebted to him for his untiring drive to improve and expand this specialty in our country. I express my appreciation to Dr. Gordon Seger for the work he has done in helping in the development of this program and for the thousands of details that he oversees in maintaining this program. And to Dr. Adolph Sahs, the new chairman of the committee, I wish good luck in a difficult but extremely important job.

Administration of the Training Grant Program in Neurology

Gordon H. Seger, Dr. P.H.

THE PROGRAM of graduate training grants administered by the National Institute of Neurological Diseases and Blindness was inaugurated in 1952, but did not get underway on any appreciable scale until July 1, 1953 because of the limited funds available. During the following 12 months, 16 grants were awarded for a total of $260,000. From this modest beginning a little less than four years ago, this program for the advanced training of teachers and investigators in the field of neurologic and sensory diseases has grown to its present proportions of 111 training program grants, involving support slightly over $3,000,000 annually.

Not only has this program grown rapidly in size, but it has also expanded materially in scope. At the present time, graduate training grants are awarded in all neurologic and sensory disease areas in which there is a recognized dearth of adequately trained personnel for academic and investigative positions. Awards are made to support training in such medical specialties as neurology, ophthalmology, otolaryngology, neuropathology, and pediatric neurology. In addition, postdoctoral basic neurologic science grants are available to support training programs in such areas as neurochemistry, neuropharmacology, neurophysiology, and neuroanatomy.

Applications for training grants are given preliminary review by an appropriate training grant committee before submission to the National Advisory Neurological Diseases and Blindness Council for final recommendation. Training grant committees, comprised of outstanding academicians appointed by the Surgeon General of the Public Health Service, have been established for each of the general fields of neurology, ophthalmology, and otolaryngology. These committees maintain current evaluation of the status of training and the training needs in their respective areas, and develop and advise on procedures to make training more effective. And, of course, they advise the Council on the support of training programs, proposed or underway.

The purpose of all training grants awarded by the National Institute of Neurological Diseases and Blindness is to assist training institutions to increase the number of adequately trained personnel available for careers as teachers and investigators. Training grants are, therefore, program grants and are made to help institutions establish, expand, and improve all aspects of their program of training in a particular field. Support is initiated on the premise that it will be continuous so long as the program is productive and a need exists for the particular type of personnel being trained.

Graduate training grant funds supplement the training institution's own support of the program. Training grant funds are used to employ additional medical staff, to provide additional trainee stipends, to purchase additional equipment and supplies needed for the training program, and to finance travel so that trainees may attend meetings and conferences. Since training grant funds are to be used supplementarily, the amount awarded to aid any individual program varies with the institution's need and the program's capacity to train. With these few introductory remarks, I would like to report in detail on training grant supported programs in clinical neurology.

Of all the major research areas encompassed in the neurologic and sensory disease field, no area was so destitute of adequately trained teachers and investigators in 1953 as was clinical neurology. At that time the number of neurologists trained annually was barely sufficient to replace those lost to the field because of retirement or death. Consequently, the first training grants were made in clinical neurology in order to meet this imperative national need. Today, grants for clinical neurology comprise almost 50 per cent of the total number of training grants made by the National Institute of Neurological Diseases and Blindness and involve a like proportion of the total training funds awarded.

In 1953, only 21 of the nation's medical schools had neurology units, many of which were not actually engaged in training neurologists. Today, at least 54 organized training programs are functioning, aided in the amount

Chief, Extramural Programs Branch, National Institute of Neurological Diseases and Blindness, Public Health Service, U.S. Department of Health, Education, and Welfare.

of $1,465,000 annually. It is estimated that through this aid, the nation's training capacity in clinical neurology has been increased from about 90 individuals in 1953 to at least 250 at the present time. It is of interest to note, from an analysis of clinical neurology training grant budgets, what needs were most essential to an expansion of this magnitude.

Of the $1,465,000 presently awarded to aid the 54 programs in clinical neurology, 83 per cent or $1,211,000 is budgeted for the support of personnel. A further breakdown of these figures shows that 40 per cent of the total awarded is budgeted for professional staff to carry out the training, 11 per cent for auxiliary staff, and 32 per cent to provide stipends to those being trained. Of the remaining 17 per cent of the total awarded, 9 per cent is utilized for miscellaneous expenses such as supplies, equipment, and travel, and the remaining 8 per cent goes to aid in paying institutional overhead costs. From these data it can be seen that, to the neurologist administering a training program, the most important needs in training teachers and investigators are a competent staff to direct the training and funds to support those who are being trained.

In terms of the actual numbers of individuals concerned, present neurology training grant funds aid in supporting 129 of the 173 professional staff engaged in training and 130 of the 217 residents involved in the 54 programs. To avoid a misunderstanding of these figures, it should be made clear that, in a considerable proportion of cases, program directors elect to utilize grant funds to pay only a portion of the salary of individual staff members and only a portion of the stipend of individual residents. As indicated above, about a quarter of the 173 professional staff engaged in training duties and 40 per cent of the residents in these programs receive no direct financial aid from these training grant funds.

The support of residents out of training grant funds is of sufficient importance to warrant detailed explanation of relevant training grant policy. It is the policy of the National Institute of Neurological Diseases and Blindness that the director of a training grant program should have freedom, within the limits of his own institution's policies, to choose the personnel he is to train and, within a liberal stipulated maximum, to set the stipend rate for those trainees to be paid in whole or in part from the training grant.

Since training grant funds are to be used supplementarily, stipends previously derived in whole or in part from institutional sources may not be transferred to the training grant budget. Training grant funds budgeted for stipends may be used to increase institutionally established stipend rates if such seems necessary. The primary purpose in granting funds for stipends, however, is to increase the number of trainees by providing additional stipends. This point is stressed in NINDB training grants, because an increase in the number of trainees not only serves to add ultimately to the total manpower pool, but also tends to lessen the purely service load on each trainee while in training. His time is thereby freed for more adequate training along academic and investigative lines.

Lastly, since the objective of the grant is to train teachers and researchers, program directors are urged to support from grant funds only those trainees who are interested in or who have demonstrated a potential for teaching and investigative careers. The program director's choice of trainees is extremely important, because the only valid measure of the success of a training grant is the program's contribution from year to year in terms of additional clinical teachers and investigators.

Many authorities believe that the organizational position of the neurology service within a medical school has an important bearing on its success in training personnel. In administering a training grant program, the Institute recognizes that medical schools vary widely in basic organizational structure. We realize that the facilities, both physical and patient material, vary as to characteristics, amount, and location, and that the concepts and educational philosophies of the individuals in charge of training programs differ. Because of these variables we do not recommend to institutions that they adopt a particular organizational structure for training. We assume, however, that the organizational pattern proposed in an application for funds is that which the institution has determined, after careful consideration, is the best for carrying out the objectives of the grant.

Of the 54 training grant programs in clinical neurology, 27, or 50 per cent, are organized under autonomous departments of neurology, 18 are located in departments of medicine, and nine are combined departments of neurology and psychiatry. Of the 18 departments of medicine, 12 have neurologic services with divisional status. In the nine programs organized under a department of neurology and psychiatry, two have divisional status. These

data must be considered with reservation, because organizational titles are not always indicative of administrative status.

In contrast to program grants, two other training program administered by the Institute involve direct awards to individual trainees, and should be touched upon to show how they can contribute to training in neurology. The first, special clinical traineeships,* are awarded to individuals who have completed the residency requirements in a specialty and desire further training in the neurologic and sensory disease field.

Special clinical traineeship stipends may be awarded for annual periods not to exceed three years, and range from $5,500 to $14,800 per annum. The specific amount is determined on the basis of qualifications and financial need of the applicant. Awards are given, for example, to pediatricians who wish to specialize in pediatric neurology, to pathologists for training in neuropathology, and to neurologists who wish to undertake highly specialized training in the clinical aspects of neuropharmacology, neurochemistry, neurophysiology, or a similar discipline. Special clinical traineeships are awarded for advanced training either in this country or abroad.

The second of these individual awards programs, special research fellowships, carries the same stipend rate, but is primarily for those who desire laboratory training or experience in a basic science area. Eligibility for a special research fellowship requires a minimum of three years of postdoctoral training or pertinent experience and is ideally suited to those who are particularly interested in the basic neurologic sciences, such as neurophysiology, neurochemistry, neuropharmacology, and neuroanatomy.

Both of these programs of individual awards, especially special clinical traineeships, can be valuable adjuncts to training programs in clinical neurology. That they are not utilized as much as they could be is probably due to the over-all scarcity of personnel. At the present time, it is not unusual for a neurologist to be enticed away from his residency before its completion by the offer of an attractive staff position in a training institution. Hopefully, as more men are trained, such pressures will decrease and institutions will find it easier to obtain thoroughly trained academicians.

I would be remiss not to mention briefly still another form of financial support that serves to strengthen a training program. It is generally agreed that it is difficult to develop a well rounded program for the training of teachers and investigators without concurrent research activities. Program directors are encouraged to develop research programs and, if needed, to apply separately for research grant support. Training grant funds may not ordinarily be used for research other than that research which is incidental to the training. The research grant program of the Institute is its largest and oldest program. It is well known to all and need not be elaborated upon at this time.

In summary, this report has briefly touched upon the entire graduate training grant program administered by the National Institute of Neurological Diseases and Blindness, with particular emphasis on the program in clinical neurology. It has indicated how financial aid can be provided to support training programs on a long-term basis. How trainees may be supported for a five or six year period until they have had time to develop into competent teachers and investigators has also been explained. Suffice it to say that, through a combination of support derived from a training grant, clinical traineeships, research fellowships, and research grants, we can aid institutions in developing outstanding teachers and investigators in the neurologic and sensory disease field.

This report has dealt mainly with policy matters and the financial aspects of grants-in-aid. There are other problems, equally or perhaps more important, because good training programs cannot be bought but must be built. You have kindly consented to attend this conference to discuss how better training programs in clinical neurology can be developed and maintained. The Institute is indebted to you for your willingness to provide counsel on such an important matter.

*As of July 1, 1957, the special clinical traineeship program has been combined with the special research fellowship program under one program of special traineeships open to both clinical and basic science personnel.

Clinical Aspects of Training in Neurology

A. B. Baker, M.D., Panel Chairman

THIS REPORT summarizes the first of a series of three panel discussions and deals with the subject of the strictly clinical component in the training of a clinical neurologist. The neurologists who served as chairmen of each of the six 15-member panel sections are as follows: Drs. Russell N. DeJong, Gilbert H. Glaser, Sidney Carter, Charles Van Buskirk, Francis M. Forster, and A. B. Baker.

Due to the broad scope of the subject, it was clearly recognized that an all-inclusive approach would be impossible. Therefore, several facets were chosen for discussion which were believed to be of paramount significance. These were reviewed by the six sections, and the following represents the general consensus.

The initial problem dealt with the minimal time a trainee should spend exclusively in the care of patients and in which periods the trainee should be so assigned. It was felt that, in the training of clinical neurologists, the minimum time which should be spent exclusively in the care of patients is between a year and a half to two years, preferably two years. Further, it was believed that the greater part of the first year should be spent in the clinical care of patients.

The next point brought under discussion was the degree of personal responsibility for the patient which should be delegated to the trainee. It was agreed that, during the clinical training period, in the presence of adequate neurologic supervision, the trainee should assume progressive responsibility for the patient aimed at achieving total patient responsibility by the end of the third year.

Attention now turned to the problem of the proper size and characteristics of in-patient load per resident. In regard to the proper size of the in-patient material, it was considered that there should be a minimum of three or four new patients for each resident per week during the time spent on the in-patient service, with an average load of eight to ten patients per resident. This should include exposure to both chronic and acute patients and should include adults of both sexes, as well as children. There should be adequate experience in the diagnosis and treatment of infectious, vascular, traumatic, neoplastic, degenerative, and metabolic disorders of the nervous system. Additional training in medicine and psychiatry is also desirable for a well trained neurologist.

The subject of the diagnostic and special procedures which should be carried out by the trainee was now considered. In the presence of adequate supervision, it is certainly desirable that the trainee become proficient in the performance and interpretation of the following procedures: 1) lumbar and cisternal puncture, 2) subdural taps in infants, 3) pneumoencephalography, 4) myelography, 5) arteriography, 6) psychologic testing, 7) testing of special senses (visual fields, calorics, and so on), 8) nerve blocks, 9) electroencephalography.

The next question dealt with the volume of emergency, out-patient, and consultative hospital service necessary for the support of a balanced neurology training program. In general, it was felt that in a neurology training program each resident should spend one-fifth of his clinical time in the out-patient service and should see a minimum average of one new and two old patients at each clinic session. Specific disease clinics such as multiple sclerosis, epilepsy, and others may be supplementary but should not be substituted for out-patient training. A neurology resident should spend a minimum of 20 per cent of his clinical training on consultation. Preferably this should be in the latter part of his neurologic training and under adequate supervision. This consultation service should not be a substitute for an in-patient service. Also, emergency room service is highly desirable.

The last problem for consideration was the minimum staff time commitment per resident which was necessary to provide adequate supervision of the clinical aspects of training in neurology. The minimum should be 12 hours of clinical and three hours of conference supervision per week for the first and second years, and four hours of clinical plus four hours of conference supervision per week during the third year of training. Finally, there should be daily direct contact between the teaching staff and the trainees.

Professor and director of the division of neurology, University of Minnesota Medical School, Minneapolis, Minnesota.

Basic Science Aspects of Training in Neurology

James O'Leary, M.D., Panel Chairman

THIS PANEL discussion dealt with the basic science component of neurology training. As in the panel discussion of clinical aspects reported on by Dr. Baker, the six sections of this particular panel were necessarily limited to the discussion of only the most important facets of basic science training in those areas believed to be involved in adequate training, namely: neuropathology, neuroanatomy, neuroroentgenology, neurophysiology, electroencephalography, neuro-ophthalmology, neuropharmacology, and neurochemistry. The chairmen were: Drs. Morris B. Bender, Ephriam Roseman, Richard B. Richter, Augustus S. Rose, Abner Wolf, and James L. O'Leary. The following is an attempt to provide a summary report of the considerations of these subjects.

The panel began with a discussion of three questions. First, which of the above basic science subjects are absolutely essential to the trainee in neurology and which are elective? Secondly, in a three-year clinical training program in neurology, how much time can be spent justifiably in attaining research proficiency and carrying out research in one or more of the basic science subjects? Thirdly, how should the time spent in the basic sciences be apportioned and coordinated with the time spent on the remaining components of the clinical program?

It was generally agreed that the average trainee in neurology arrives with an inadequate knowledge of the basic science disciplines, but, in general, is best prepared in neurophysiology and clinical chemistry. Of the subjects listed as basic, there was unanimity of opinion that neuro-ophthalmology and neuroradiology should be incorporated into the clinical aspects of the training program. Some would add neuro-otology to this list.

As was reported previously, there was general agreement that at least two years of clinical neurology are essential to the success of any three-year program, and, further, at least six months of clinical training should initiate the residency. However, time should be provided during which the trainee is released from his principal clinical responsibilities to devote time to the following subjects: neuroanatomy, neuropathology, electroencephalography, and neurophysiology. The desirable goal in all such training is to attain a practical familiarity with the subject matter, since the large majority felt that, with the exception of participation in clinical investigations while on the in-patient service, there is no time in a three-year program for attaining research proficiency by detached basic science investigation. Finally, the fields of neurochemistry and neuropharmacology, although of the utmost significance in basic neurologic research, play a relatively smaller role in a three-year program.

Attention was now directed toward consideration of the best methods of teaching each of the above basic science subjects in the clinical training program, and who should have the primary responsibility for determining the over-all content and teaching approach for each of these subjects. Further, there was discussion of the measures which should be taken to provide day-by-day correlation of these basic sciences with clinical case material.

Over-all emphasis was placed upon flexibility of programs. It is reasonable to assume that in one program the orientation of the director, the personnel, and the facilities available may emphasize one basic science subject, for example, neuropathology or electroencephalography, even though all of the subjects listed above are essential components of any balanced program. It was also agreed that the program director should be able to individualize the decision as to the particular basic science needs of a trainee. However, there was a division of opinion on whether he should decide the content of material presented by teachers in associated basic science departments.

Although it was the general feeling that neuroanatomy, neuropathology, electroencephalography, and neurophysiology should be taught to the trainee in large part during an isolated block of time, it was emphasized that these subjects should also be stressed from the beginning of the training program. This would take place in addition to neuro-ophthalmology and neuroradiology, plus some emphasis on

Professor of neurology, Washington University Medical School, St. Louis, Missouri.

neurochemistry and neuropharmacology. This may be done by bedside training, weekly conferences, and special conferences utilizing patients selected especially for interdisciplinary training. Basic science teachers and appropriate clinical specialists should be included in the special conferences if available.

Certain teaching aids can be made directly available to the residents. These include bringing the electroencephalographic tracings of current cases to the ward and providing models and diagrams illustrating the anatomy and physiology of the nervous system. Sections of brains from recent necropsies are also useful for establishing clinical pathologic correlations. However, some participants were anxious to avoid overstressing these aspects of correlated training, since there is a saturation point past which the residents' available time will be exhausted.

Electroencephalography cannot be taught by reading tracings alone. Adequate training would require application of electrodes, the running of selected records, study of artifacts, and references to available atlases. Much of the same may be said of electromyography and of electrodiagnostic methods in denervation, if they, too, are to be taught.

Neurochemistry is best taught at bedside conferences and in formal lectures, both given from the perspective of metabolic and endocrine disturbances. Neuropharmacology cannot well be separated from neurochemistry, but current information concerning toxicity and other data applying to recent drugs should be available immediately for reference purposes.

Neuro-ophthalmology needs emphasis, especially with respect to the conduct of the visual field examination. It may also be desirable to call upon the services of an ophthalmologist with special interests in neuro-ophthalmology, if available, as a consultant in all cases.

Lastly, in one section the need for emphasis upon the neurology of behavior was stressed. It was felt that this should be continued throughout the program. This includes concepts of biologic intelligence, of conditioned reflexology, and of the effect of a neurologic handicap upon personality structure.

All this should be directed toward developing the incentive to continue training into the fourth, fifth, and even sixth years. This will permit special skills and particularly research proficiency to be acquired by selected individuals.

CONFEREES

Adams, Raymond D.
Aird, Robert B.
Aita, John A.
Aring, Charles D.
Baker, A. B.
Bender, Morris B.
Bieter, Raymond N.
Boshes, Benjamin
Brown, Joe
Carter, Sidney
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Cohen, Maynard
Comroe, Julius H.
De Jong, Russell N.
Denny-Brown, Derek E.
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Madden, John J.
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Noran, Harold H.
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Richter, Richard B.
Rose, Augustus S.
Roseman, E.
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Scheinberg, Peritz
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Watson, C. Wesley
Williams, Robert L.
Wolf, Abner
Wolff, Harold G.
Wortis, S. Bernard
Zimmerman, H. M.

Administrative Aspects of Training in Neurology

Francis M. Forster, M.D., Panel Chairman

BELOW is a summary of the third and last panel discussion, in which an attempt was made to outline the major administrative factors associated with neurology training. The following is a list of the neurologists who acted as section chairman: Drs. Russell N. DeJong, Gilbert H. Glaser, Sidney Carter, Charles Van Buskirk, Francis M. Forster, and A. B. Baker.

In these discussions it soon became obvious that those responsible for neurologic education are keenly aware of the trends of medical education in general. There are three outstanding characteristics of American medical education. The first of these is the importance of clinical training, the second is the vertical teaching program carrying subjects through as many years of education as possible, and the third is the use of integrated teaching at both the undergraduate and clinical training levels.

In regard to the importance of clinical teaching, the relationship between teacher and student cannot be overemphasized. Medicine is no longer predominantly didactic and is not a matter of "a fountainhead filling empty heads." The long series of lectures in the amphitheater has given way to bedside and out-patient training, with emphasis on the importance of the student-patient and the resident-physician relationships. While neurology has long been engaged in this active teaching method, even with the full use of clinical material there is a slight shift toward the didactic in our graduate training programs. It was emphasized that graduate teaching today may be overloading the residents with conferences. We must stress individual patient studies.

In neurologic education there are characteristics of the same vertical type of teaching that our confreres in other fields have been stressing. Because neurologists are modest, scholarly people, this point has not been belabored, but vertical teaching has been applied in neurology for a long time. Vertical teaching in neurology is implemented through courses in neuroanatomy, neuropathology, and neurophysiology, either as autonomous courses or as parts of the major subjects given in the first and second years of medical school. Included also is the clinical instruction in neurology given in the junior and senior years. Neurology, therefore, extends in continuity through the four year undergraduate program.

Experience has demonstrated the importance of eliciting active teaching interest of the preclinical faculty in the broad field of neurology as a prelude to developing the basic knowledge necessary for understanding the content of clinical conferences. Moreover, the neurologic conferences should be attended by the interested preclinical faculty as well as the radiologists, neurosurgeons, psychiatrists, internists, and pediatricians. When medical schools begin to move in the direction of integrated and coordinated teaching, the chairman of the curriculum committee will then be pleasantly surprised to learn that neurologists have already been participating in integrated teaching for some time.

Thus neurology is assuming leadership in the transformation toward more effective methods of medical education. It would now be important to consider first, how the activities of neurology can be coordinated with allied departments to develop adequately its function of service, training, and research; and second, the responsibility of the neurologic service for satisfying teaching and service demands outside its immediate department.

These points establish the parameters of neurology in its broadest aspects. Numerous demands in the realm of teaching are made upon the neurologic disciplines: 1) by the preclinical sciences of neuroanatomy, neuropathology, neurochemistry, neuropharmacology, and neurophysiology; 2) by the clinical fields of neurosurgery, medicine, psychiatry, pediatrics, physical medicine and rehabilitation; 3) by the ancillary fields of nursing, occupational and physical therapy, and psychology.

Demands for service include consultation on other services, out-patient responsibilities, and special laboratory requests. The electroencephalographic laboratories in most institutions are under the aegis of the department of neurology, and there is often a research laboratory of some special type—perhaps biochemical—for performing tests which supplement the routine hospital services.

Dean and professor of neurology, Georgetown University Medical School, Washington, D.C.

In reviewing these demands, the group proposed that, within the limits of the staff and personnel, it is the responsibility of the neurologic service to assist in training other personnel when the demand exists. Thus, neurology must coordinate its activities closely with all other departments. This integration can be accomplished best by developing coordinated activities in areas of common interest. This can be achieved in the area of service by tendering neurologic consultation and by joint conferences. In the training area, residents can be accepted from other services on a rotating basis and combined conferences can be organized.

Frequently the research interests in neurology are shared jointly with the basic sciences. There is no one administrative arrangement which can best satisfy these needs, since common areas of interest exist between neurology and almost all clinical and basic divisions of hospital and medical school. This is particularly true for neurosurgery, psychiatry, medicine, pediatrics, and physical medicine, and it will be to the advantage of neurology to develop the methods of collaboration and coordination mentioned above in all instances.

The status of the head of neurology in the over-all administration of the medical school is a point of major significance in relation to the coordinated activities of neurology with the other departments. Since the parameters of neurology are broad, the demands are great, and the responsibilities are heavy, it is necessary for neurology to have vested in it adequate administrative authority to cope with such demand in a continuing series of interdepartmental relationships.

Next the question arose as to who should have the primary responsibility in the care of the neurologic patients on in-patient and out-patient services. From the administrative standpoint, responsibility must rest in the hands of the neurology staff and, in turn, must be delegated to its own residents. In order for the neurology resident to have the primary responsibility and the staff assume the ultimate responsibility, it is necessary to have an autonomous bed service. The resident must learn to bear responsibility in the doctor-patient relationship as a representative of his staff neurologists. Only a disciplined group operating on its own responsibility can hope to provide the most efficient neurologic service.

The final problems brought up for discussion dealt with the ideal academic and hospital administrative organization for neurology, and the necessary minimum of institutional support for clinical neurology with regard to finances (proportion of total budget), physical facilities, and administrative control.

The head of neurology in a medical school should be a full professor. His salary should be consistent with his rank and should be derived from an institutional budget. It is recommended that neurology should be given independent departmental service status but, if it is set up as a division, it should operate with the greatest possible autonomy in respect to appointments, budget, and educational program. There must be direct contact with the dean. Also, there must be representation on a faculty body so that information as to administrative decisions in the hospital and school will be available immediately to the head of neurology. As to hospital administrative organization, the head of neurology should be chief of in-patient and out-patient services and should be on the governing body of the medical staff.

The question of the proportion of the total budget which should be met by the institution was discussed at considerable length. The panel recommended that the institutional contribution should be at least one-third of the total budget of the department. Deliberation concerning the cost of establishing a new department led to the following conclusions: The minimum institutional financial support for clinical neurology should cover the salary for the head of the department, salary for clerical and technical assistance, funds for administrative expenses for the department, a solid commitment for a second staff member of the department as the program develops, and a hospital allotment for the salaries of neurologic residents. In regard to physical facilities, the minimum would include beds for patients, space for the department head and ancillary personnel, laboratory space, and out-patient facilities. Areas for the teaching of electroencephalography and basic sciences are also necessary, if not already available in the hospital or medical school. Finally, to reemphasize a point already made, autonomy of departmental or divisional status and a separate service in the hospital are absolutely essential.

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DECEMBER 1957

Prize Essay Deadline Now at Hand

The deadline for the receipt of manuscripts to be entered in the Academy prize essay contest, open only to AAN junior members, is Dec. 20, 1957. Established by the Woman's Auxiliary of the Academy, an award of $200 is made to the junior AAN member who has submitted the best unpublished essay dealing with any phase of neurology. The winning manuscript will be read by the author at the coming annual meeting of the Academy in Philadelphia (April 21-26). Also, the author's transportation fare to the meeting is to be paid by the Academy. The AAN reserves the right to publish the winning manuscript, which is selected by a special committee.... Manuscripts must be typewritten, double-spaced, and submitted in quadruplicate to Mrs. J. C. McKinley, Executive Secretary, American Academy of Neurology, 3501 East 54th Street, Minneapolis 17, Minn.

Research on Allergic Encephalomyelitis Discussed at Bethesda

The controversial topic of experimental allergic encephalomyelitis provided the theme for a two-day interdisciplinary symposium, held October 19-20 under the auspices of the National Institute of Neurological Diseases and Blindness. Sixteen scientists presented papers on the clinicopathologic correlations observed, the etiologic and immunologic aspects of the problem, which were discussed under the co-chairmanship of Abner Wolf, Jordi Folch-Pi, Byron H. Waksman, and Ernest Witebsky.... Among the other speakers were Leon Roizin, Hirotsugu Shiraki (Tokyo, Japan),[1] Richard M. Condie, Marjorie Lees, Johanna Lee, Elizabeth Roboz, Marian W. Kies, Howard A. Schneider, Merrill W. Chase, Murray Lipton, Philip Y. Paterson, Frederick C. Robbins, and Ellsworth C. Alvord, Jr..... Forty-nine additional conferees participated, among them several visiting scientists from other countries: Antonio Allegranza (Italy),[1] Jack Colover (England), J. Godwin Greenfield (England), Robert Heitmann (Germany), E. Weston Hurst (England), Edgar Lederer (France), Jerzy Olszewski (Canada), Edith Pette (Germany), and Michel Vulpe (Canada).... Besides the presentations on the experimental aspects of allergic encephalomyelitis, there were epidemiologic reports which suggested a high incidence of encephalomyelitis in Japan in individuals over the age of ten who had been immunized with rabies vaccine. Here the pathology, a

[1]Participation aided by a grant from Smith, Kline & French Foundation.

patchy demyelinization, was described as resembling that of multiple sclerosis. On the other hand, multiple sclerosis itself was reported to be quite rare in Japan, but to have an unequal distribution in Australia, being absent in some parts and prevalent in others.... On Saturday evening, October 19, 53 of the conferees and guests gathered at an informal dinner at the National Naval Medical Center Commissioned Officers Club in Bethesda to hear a comprehensive review by Raymond D. Adams of the pathologic changes found in various inflammatory and demyelinating disorders of the nervous system, ranging from the highly inflammatory process of acute hemorrhagic encephalomyelitis to the slowly degenerative processes which show minimum inflammatory reactions.... The symposium was sponsored by the National Advisory Neurological Diseases and Blindness Council, by a grant award to a committee headed by Ellsworth C. Alvord, Jr. (Baylor University) and Philip Y. Paterson (New York University), Elizabeth Roboz (Georgetown University) and Marian W. Kies (Bethesda), who organized the symposium in collaboration with Henry A. Imus (Bethesda).... The proceedings of this symposium will be published as a monograph by Charles C Thomas, Publisher.

Kernicterus Featured At AACP Meeting

The opening event of the annual meeting of the American Academy for Cerebral Palsy in New Orleans, on November 24-27, 1957, was a special three-hour scientific session on "The Role of Erythroblastosis and Kernicterus in Cerebral Palsy".... The symposium, chaired by Chester A. Swinyard and moderated by Pearce Bailey and Nicholson J. Eastman, president of the AACP, was sponsored by the Association for the Aid of Crippled Children, the National Institute of Neurological Diseases and Blindness, the National Society for Chippled Children and Adults, and the United Cerebral Palsy Association.... The purpose of the symposium, as organized by the society's research committee, was to coordinate scattered data from experimental studies on the pathogenesis of hyperbilirubinemia and kernicterus in the cerebral palsied child.... Among the participants in the program were Richard L. Day, Lois Johnson, Wolf W. Zuelzer, Webb E. Haymaker, Angel Pentschew, Nathan Malamud, Donald B. Lindsley, William G. Hardy, Meyer A. Perlstein, Sidney Carter, T. F. McNair Scott, Harold Westlake, Leslie B. Hohman, and Arnold S. Breakey.... Plans are under way for the publication of the symposium proceedings as a monograph.... This special scientific session was followed by the regular AACP program and social events, the latter including a display of southern hospitality in New Orleans, visits to the French Quarter, the New Orleans harbor in the city yacht "Good Neighbor," brunch in an Old Southern home, and a tour of ante bellum homes.

Windle Wins Weinstein Award

At the eighth annual convention of the United Cerebral Palsy Association in St. Louis (October 31-November 3), the Max Weinstein Award, a silver plaque and a check for $1000, was made to William F. Windle, chief

of the Laboratory of Neuroanatomical Sciences, National Institute of Neurological Diseases and Blindness. This award is made annually for outstanding achievement in basic research related to cerebral palsy. Previous winners are: Abner Wolf, S. P. Hicks, H. W. Magoun, Seymour S. Kety, Paul Yakovlev, and Louis V. Flexner. Presentation of this year's award was made by Dr. Kety (winner in 1954), who, in conferring the honor on Dr. Windle, eulogized him on two counts: First, because of his contributions to neurologic research through his investigations in central nervous tissue regeneration and other fields, and secondly, because he had blazed a trail for the study of experimental cerebral palsy by his studies of neonatal asphyxia in cats and guinea pigs, investigations which Windle now has extended to monkeys in an NINDB project on asphyxia neonatorum in Puerto Rico. The asphyxia studies, according to Dr. Kety, "have a double significance since they preceded by years (1948) the present emphasis on neurologic casualties arising in the perinatal period, and even antedated the rising tide of public interest in cerebral palsy."... The principal guest speaker at the United Cerebral Palsy convention was Department of Health, Education, and Welfare Secretary Marion B. Folsom, who called for a more united front in neurologic research.

Neurologic Clinic Visited in Turin

In Turin, a serene metropolis in northern Italy, high in urban sophistication and in industrial production (home of the Fiat auto works), your reporter visited the Clinic for Diseases of the Nervous System of the University of Turin. The visit was made with one of the clinic's many distinguished alumni, Cosimo Ajmone Marsan, now residing in Bethesda, Maryland.... The Turin clinic is a modernly equipped and expertly staffed neurologic teaching and research center, of which Professor Dino Bolsi is the director. It comprises a neurologic section of 90 beds, with a blueprint for 50 more, and a neurosurgical section of 40 beds under Dr. G. Kluzer, chief, and Dr. V. A. Fasano, which is equipped with air conditioned rooms, oxygen outlets, teaching microphones, and facilities for high standard electrocorticography. Moreover, the clinic has well equipped research laboratories for both clinical and basic research[2].... After inspection of the patient areas, we were guided personally in our visit to the research laboratories by Dr. V. Bergamini, director of the laboratories in EEG, EMG, and neurophysiology. He introduced us to Dr. A. Sicuro, director, and his staff, who conduct an active service in neuroradiology, a strong specialty throughout Italy; to Dr. R. Scarzella, director, and his associates of the biochemistry and serology laboratories, which also have facilities for chromatography. Next, we met Drs. F. R. Grattarola and D. Schiffer, who, with a competent staff,

[2]A few samples of their research projects: cinematographic cerebral angiography, polygraphic studies of epilepsy, single motor unit investigations in muscular diseases, protein metabolism in degenerative diseases, genetic studies of amino acids in urine, cytologic patterns in cerebral neoplasia, senile ependymopathies, lipasic activity of the brain, and the measurements of the metabolic variation protein content of single nerve cells.

direct the laboratories of histopathology and histochemistry, respectively. Then we proceeded to meet Dr. G. Gomirato, director of the laboratory of biophysics, who also has the rank equivalent to associate professor. Dr. Bergamini demonstrated his own projects in neurophysiology, where four postgraduate students are working together, as well as a full-time electronics engineer. Finally, our tour took us to Dr. E. Arian to learn about his program in clinical psychology and psychophysiology.... The research projects under way at the clinic are imaginative, numerous, and wide in range, consistent in general with the lines of neurologic research in the U. S. While the thinking at the clinic is essentially neurologic, yet like many of the clinics in Europe, training is provided in both neurology and psychiatry. The program consists of three-year clinical clerkships, with didactic instruction in the basic sciences for each discipline.

Title Deadlines For AAN Meeting Gilbert H. Glaser, scientific program chairman, and Louis D. Boshes, chairman of exhibits, wish to remind AAN members that the deadline for submission of titles and abstracts of scientific papers and demonstrations to be presented at the tenth annual meeting of the American Academy of Neurology, to be held in Philadelphia, Pa. (April 21-26), is January 8, 1958. Titles and abstracts of papers (not to exceed 150 words) should be forwarded to Dr. Gilbert H. Glaser, Yale University School of Medicine, New Haven 11, Conn.... Titles and 150-word abstracts of exhibits or demonstrations should be submitted to Dr. Louis D. Boshes, Department of Neurology and Psychiatry, Northwestern University Medical School, 303 East Chicago Avenue, Chicago 11, Ill.... If motion pictures are to be shown, the film size, sound requirements, or special projection needs should be indicated.

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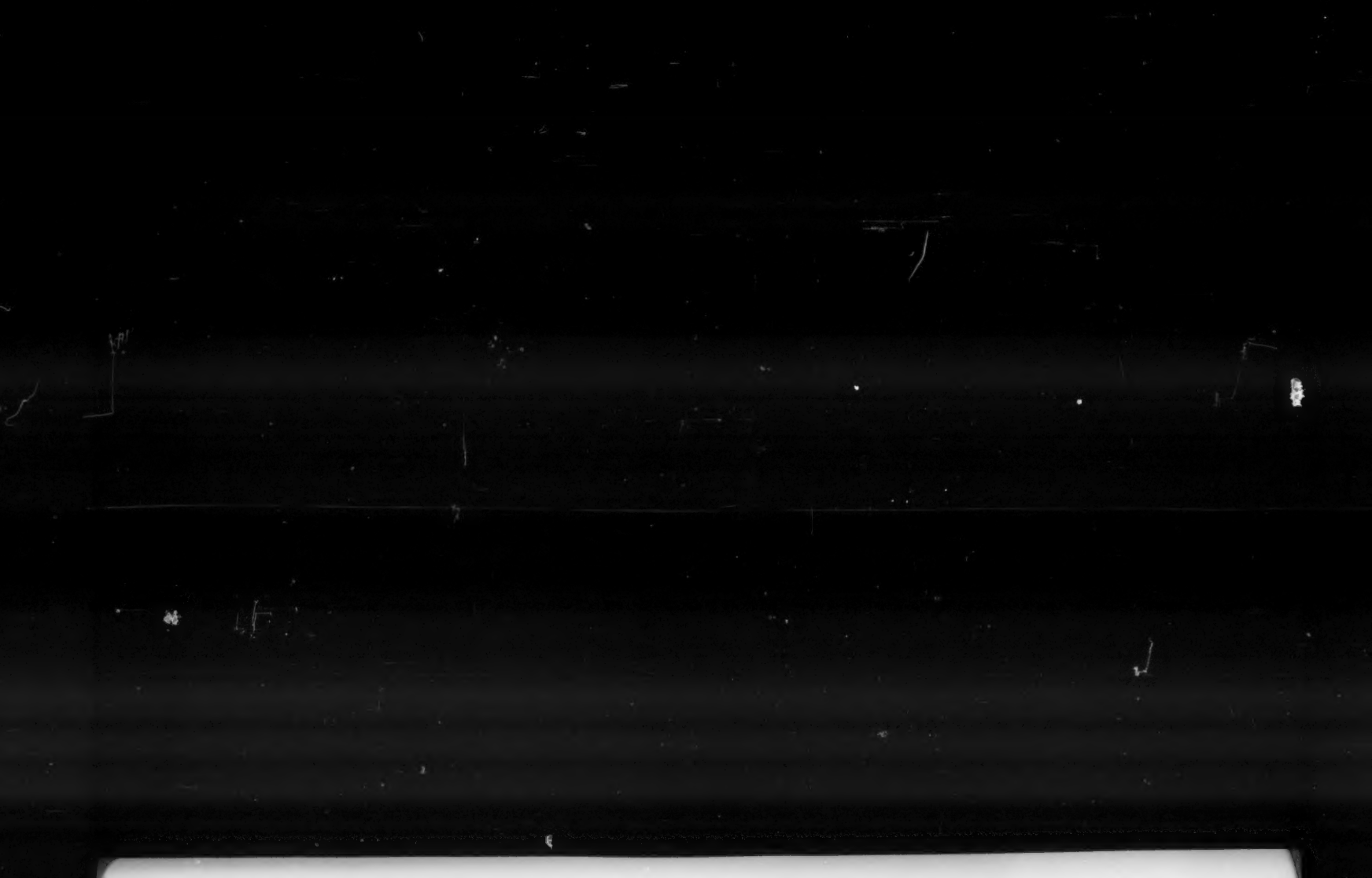
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